STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 150191

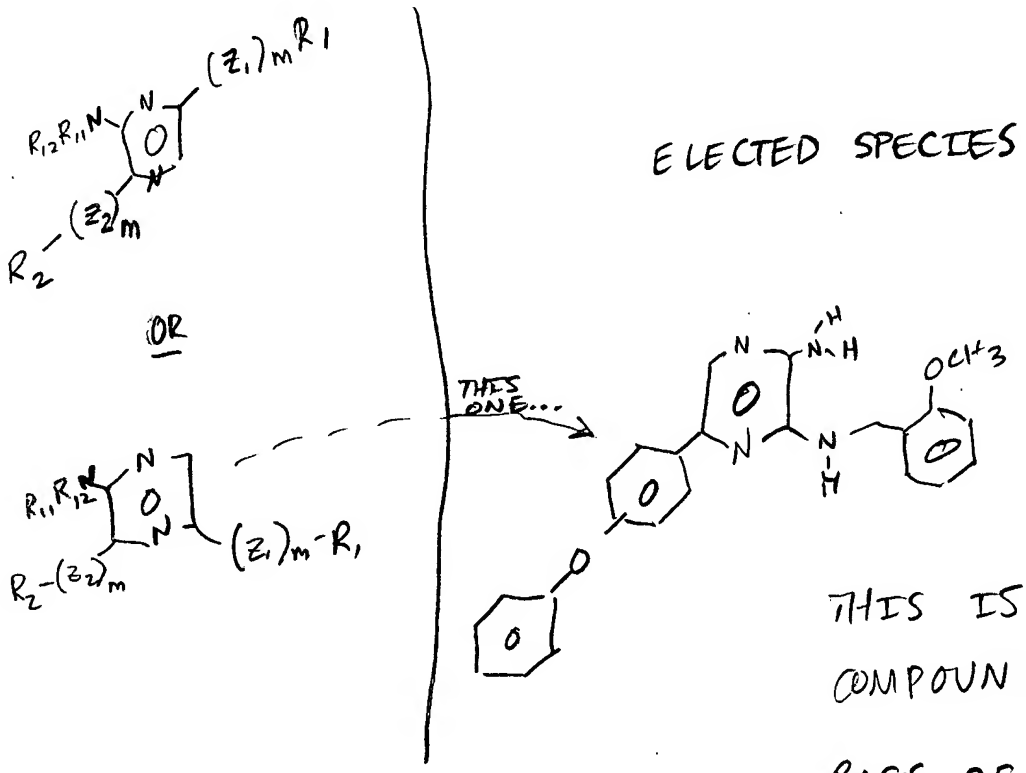
TO: Zachary Tucker
Location: REM 5c04/5C18
Art Unit: 1624
April 7, 2005

Case Serial Number: 10/602560

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes



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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 7 Apr 2005  VOL 142 ISS 15
FILE LAST UPDATED: 6 Apr 2005  (20050406/ED)

 This file contains CAS Registry Numbers for easy and accurate
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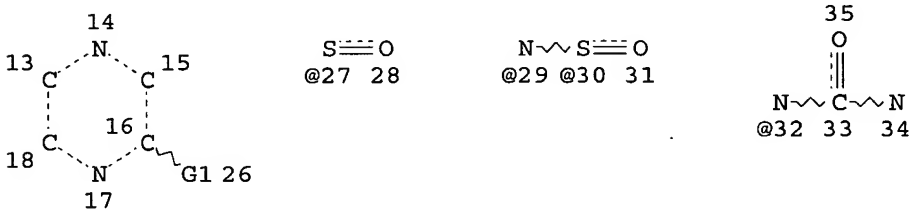


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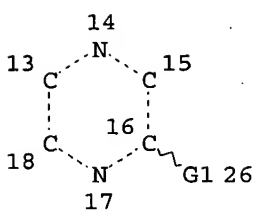

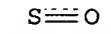

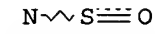

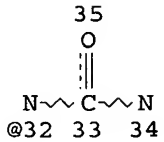

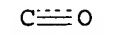

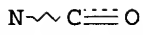

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NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE

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L23 ANSWER 1 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:1009249 HCAPLUS
DOCUMENT NUMBER: 141:90
TITLE: Targeting proteasome inhibition in hematologic malignancies
AUTHOR(S): Hideshima, Teru; Richardson, Paul G.; Anderson, Kenneth C.
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA
SOURCE: Reviews in Clinical and Experimental Hematology (2003), 7(2), 191-204
CODEN: RCEHFB; ISSN: 1127-0020
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Proteasome inhibitors represent potential novel anti-cancer therapy. These agents inhibit the degradation of multi-ubiquitinated target proteins mediating cell cycle progression, apoptosis, NF-.vkappa.B

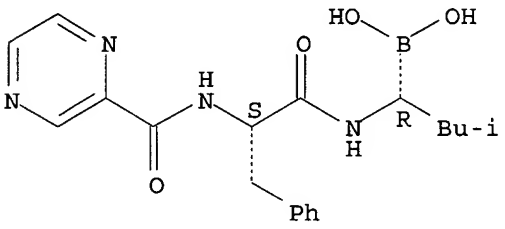
activation, inflammation, cell cycle **regulatory** proteins such as cyclins and cyclin dependent **kinase** inhibitors, as well as immune surveillance; and **regulate** anti-apoptosis and cell cycle progression. Proteasome inhibitors also directly induce caspase-dependent apoptosis of tumor cells, despite the accumulation of p21 and p27 and irresp. of the p53 wild type or mutant status. Recent studies demonstrate that PS-341, peptide boronate, has remarkable anti-tumor activity in preclin. and clin. studies, not only in multiple myeloma but also in other malignancies.

IT **179324-69-7**, PS-341
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of PS-341, a proteasome inhibitor, on human tumor cell)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:908573 HCAPLUS

DOCUMENT NUMBER: 140:192446

TITLE: The proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571

AUTHOR(S): Yu, Chunrong; Rahmani, Mohamed; Conrad, Daniel; Subler, Mark; Dent, Paul; Grant, Steven

CORPORATE SOURCE: Departments of Medicine, Radiation Oncology, Biochemistry, Microbiology, Human Genetics, and Pharmacology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, USA

SOURCE: Blood (2003), 102(10), 3765-3774
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Interactions between the proteasome inhibitor bortezomib and histone deacetylase inhibitors (HDIs) have been examined in Bcr/Abl+ human leukemia cells (K562 and LAMA 84). Coexposure of cells (24-48 h) to minimally toxic concns. of bortezomib + either suberoylanilide hydroxamic acid (SAHA) or sodium butyrate (SB) resulted in a striking increase in mitochondrial injury, caspase activation, and apoptosis, reflected by caspases-3 and -8 cleavage and poly(ADP-ribose) polymerase (PARP) degradation These events were accompanied by down-**regulation** of the Raf-1/mitogen-induced extracellular **kinase** (MEK)/extracellular signal-related **kinase** (ERK) pathway as well as diminished

expression of Bcr/Abl and cyclin D1, cleavage of p21CIP1 and phosphorylation of the retinoblastoma protein (pRb), and induction of the stress-related **kinases** Jun **kinase** (JNK) and p38 mitogen-activated protein **kinase** (MAPK). Transient transfection of cells with a constitutively active MEK construct significantly protected them from bortezomib/SAHA-mediated lethality. Coadministration of bortezomib and SAHA resulted in increased reactive oxygen species (ROS) generation and diminished nuclear factor κB (NF-κB) activation; moreover, the free radical scavenger L-N-acetylcysteine (LNAC) blocked bortezomib/SAHA-related ROS generation, induction of JNK and p21CIP1, and apoptosis. Lastly, this regimen potently induced apoptosis in STI571 (imatinib mesylate)-resistant K562 cells and CD34+ mononuclear cells obtained from a patient with STI571-resistant disease, as well as in Bcr/Abl- leukemia cells (eg, HL-60, U937, Jurkat). Together, these findings raise the possibility that combined proteasome/histone deacetylase inhibition may represent a novel strategy in leukemia, including apoptosis-resistant Bcr/Abl+ hematol. malignancies.

IT **137632-07-6**, Extracellular signal-**regulated kinase** 1 **137632-08-7**, Extracellular signal-**regulated kinase** 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571 in relation to signaling and survival pathways)

RN 137632-07-6 HCAPLUS
CN Kinase (phosphorylating), protein, ERK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

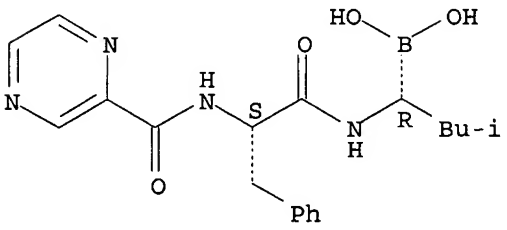
RN 137632-08-7 HCAPLUS
CN Kinase (phosphorylating), protein, ERK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **179324-69-7**, Bortezomib
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571 in relation to signaling and survival pathways)

RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:907873 HCAPLUS
DOCUMENT NUMBER: 140:174642

TITLE: Proteasome inhibitor PS-341 abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in multiple myeloma

AUTHOR(S): Hideshima, Teru; Chauhan, Dharminder; Hayashi, Toshiaki; Akiyama, Masaharu; Mitsiades, Nicholas; Mitsiades, Constantine; Podar, Klaus; Munshi, Nikhil C.; Richardson, Paul G.; Anderson, Kenneth C.

CORPORATE SOURCE: Dana-Farber Cancer Institute and Harvard Medical School, Department of Adult Oncology, Jerome Lipper Multiple Myeloma Center, Boston, MA, 02115, USA

SOURCE: Oncogene (2003), 22(52), 8386-8393
CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Proteasome inhibitor PS-341 is one of the most promising novel agents against multiple myeloma (MM). We have previously shown that PS-341 inhibits IL-6 triggered phosphorylation of extracellular signal-**regulated kinases** (ERK) 1/2 (also known as p42/44 mitogen-activated protein **kinases**) in MM cells. In this study, we further examined whether clin. achievable concns. of PS-341 could inhibit IL-6 triggered signaling cascades in MM. We found that PS-341 inhibited not only ERK, but also signal transducers and activators of transcription (STAT) 3 as well as Akt phosphorylation. Since gp130 (CD130) dimerizes and is phosphorylated after IL-6 binding to gp80 (IL-6 receptor), we hypothesized that gp130 could be involved in PS-341-induced blockade of signaling cascades mediating MM cell growth, survival, and drug resistance in the bone marrow (BM) microenvironment. In this study, we first demonstrate that PS-341 induces downregulation of gp130 in a time- and dose-dependent manner in vitro, prior to MM cell death. Conversely, downregulation of gp130 is completely abrogated by the pan-caspase inhibitor Z-VAD-FMK, suggesting that downregulation of gp130 is mediated via caspase activation. Z-VAD-FMK also abrogates the inhibitory effect of PS-341 on IL-6-triggered signaling cascades. Importantly, we demonstrate that phosphorylation of ERK, STAT3, and Akt in MM.1S cells induced by either exogenous IL-6 or by binding of MM cells to BM stromal cells is abrogated by PS-341. These studies, therefore, define another novel mechanism whereby PS-341 can overcome the growth and survival advantage in MM cells conferred by the BM milieu. Importantly, this effect on cytokine-induced gp130 signaling cascades may account, at least in part, for the remarkable preclin. sensitivity and clin. responses achieved in MM with PS-341 treatment.

IT **137632-07-6**, Extracellular signal-**regulated kinase** 1 **137632-08-7**, Extracellular signal-**regulated kinase** 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteasome inhibitor PS-341 abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in multiple myeloma)

RN 137632-07-6 HCAPLUS

CN Kinase (phosphorylating), protein, ERK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 137632-08-7 HCAPLUS

CN Kinase (phosphorylating), protein, ERK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

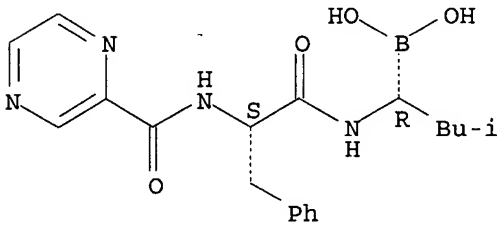
IT **179324-69-7**, PS-341
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(proteasome inhibitor PS-341 abrogates IL-6 triggered signaling cascades via caspase-dependent downregulation of gp130 in multiple myeloma)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L23 ANSWER 4 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:683094 HCAPLUS

DOCUMENT NUMBER: 139:270492

TITLE: Proteasome inhibitors disrupt the unfolded protein response in myeloma cells

AUTHOR(S): Lee, Ann-Hwee; Iwakoshi, Neal N.; Anderson, Kenneth C.; Glimcher, Laurie H.

CORPORATE SOURCE: Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, MA, 02115-6017, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(17), 9946-9951
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

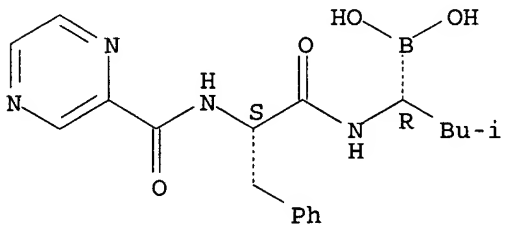
LANGUAGE: English

AB Novel agents that target the proteasome, a proteolytic complex responsible for the degradation of ubiquitinated proteins, have demonstrated remarkable therapeutic efficacy in multiple myeloma, a plasma cell malignancy. However, the mechanism by which these compds. act remains unknown. A signaling pathway called the unfolded protein response (UPR) allows cells to handle the proper folding of proteins. The transcription factor XBP-1, a **regulator** of the UPR, is also required for plasma cell differentiation, suggesting a link between the UPR and plasma cell differentiation. Here we show that proteasome inhibitors target XBP-1 and the UPR in myeloma cells. Proteasome inhibitors suppress the activity of the transluminal endoplasmic reticulum endoribonuclease/**kinase**, IRE1α, to impair the generation of the active, spliced XBP-1 species and simultaneously stabilize the unspliced species that acts as a dominant neg. Myeloma cells rendered functionally deficient in XBP-1 undergo increased apoptosis in response to endoplasmic reticulum stress. Identification of compds. that target the activity of IRE1α/XBP-1 may yield novel therapies for the treatment of multiple myeloma and other malignancies that rely on an intact UPR.

IT **179324-69-7**, PS-341
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(proteasome inhibitors disrupt the unfolded protein response in myeloma

cells by targeting the activity of IRE1/XBP-1)
RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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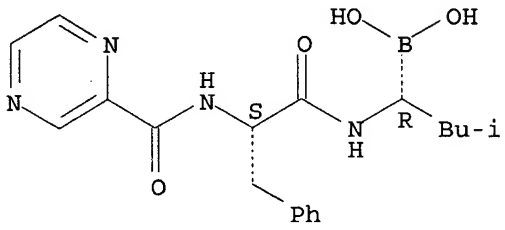
L23 ANSWER 5 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:366131 HCAPLUS
DOCUMENT NUMBER: 139:131348
TITLE: JNK-dependent Release of Mitochondrial Protein, Smac, during Apoptosis in Multiple Myeloma (MM) Cells
AUTHOR(S): Chauhan, Dharminder; Li, Guilan; Hideshima, Teru; Podar, Klaus; Mitsiades, Constantine; Mitsiades, Nicholas; Munshi, Nikhil; Kharbanda, Surender; Anderson, Kenneth C.
CORPORATE SOURCE: Dana Farber Cancer Institute, Department of Medical Oncology, The Jerome Lipper Multiple Myeloma Center, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (2003), 278(20), 17593-17596
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Smac, second mitochondria-derived activator of caspases, promotes apoptosis via activation of caspases. Previous studies have shown that c-Jun NH2-terminal **kinase** (JNK) is involved in **regulating** another mitochondrial protein, cytochrome c during apoptosis; however, the role of JNK in the release of mitochondrial Smac is unknown. Here we show that induction of apoptosis in multiple myeloma (MM) cells is associated with activation of JNK, translocation of JNK from cytosol to mitochondria, and release of Smac from mitochondria to cytosol. Blocking JNK either by dominant-neg. mutant (DN-JNK) or cotreatment with a specific JNK inhibitor, SP600125, abrogates both stress-induced release of Smac and induction of apoptosis. These findings demonstrate that activation of JNK is an obligatory event for the release of Smac during stress-induced apoptosis in MM cells.
IT **179324-69-7**, PS-341
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(JNK-dependent release of mitochondrial protein, Smac, mitochondria to cytosol during 2ME2- and PS-341-induced apoptosis in multiple myeloma cells)
RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-

[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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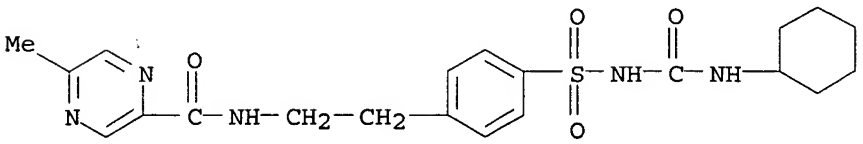
L23 ANSWER 6 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:355263 HCAPLUS
DOCUMENT NUMBER: 139:173589
TITLE: 5-Amino-imidazole carboxamide riboside increases glucose transport and cell-surface GLUT4 content in skeletal muscle from subjects with type 2 diabetes
AUTHOR(S): Koistinen, Heikki A.; Galuska, Dana; Chibalin, Alexander V.; Yang, Jing; Zierath, Juleen R.; Holman, Geoffrey D.; Wallberg-Henriksson, Harriet
CORPORATE SOURCE: Department of Surgical Sciences, Karolinska Hospital, Karolinska Institutet, Stockholm, Swed.
SOURCE: Diabetes (2003), 52(5), 1066-1072
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AMP-activated protein **kinase** (AMPK) activation by AICAR (5-amino-imidazole carboxamide riboside) is correlated with increased glucose transport in rodent skeletal muscle via an insulin-independent pathway. We determined in vitro effects of insulin and/or AICAR exposure on glucose transport and cell-surface GLUT4 content in skeletal muscle from nondiabetic men and men with type 2 diabetes. AICAR increased glucose transport in a dose-dependent manner in healthy subjects. Insulin and AICAR increased glucose transport and cell-surface GLUT4 content to a similar extent in control subjects. In contrast, insulin- and AICAR-stimulated responses on glucose transport and cell-surface GLUT4 content were impaired in subjects with type 2 diabetes. Importantly, exposure of type 2 diabetic skeletal muscle to a combination of insulin and AICAR increased glucose transport and cell-surface GLUT4 content to levels achieved in control subjects. AICAR increased AMPK and acetyl-CoA carboxylase phosphorylation to a similar extent in skeletal muscle from subjects with type 2 diabetes and nondiabetic subjects. Our studies highlight the potential importance of AMPK-dependent pathways in the **regulation** of GLUT4 and glucose transport activity in insulin-resistant skeletal muscle. Activation of AMPK is an attractive strategy to enhance glucose transport through increased cell surface GLUT4 content in insulin-resistant skeletal muscle.

IT **29094-61-9**, Glipizide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(5-amino-imidazole carboxamide riboside increases insulin-stimulated glucose transport and cell-surface GLUT4 content in skeletal muscle from subjects with type 2 diabetes)

RN 29094-61-9 HCAPLUS
CN Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:300895 HCAPLUS
DOCUMENT NUMBER: 138:321288
TITLE: Preparation of 2- and 4-aminopyrimidines N-substituted by a bicyclic ring for use as kinase inhibitors in the treatment of cancer
INVENTOR(S): Nagarathnam, Dhanapalan; Wang, Chunguang; Chen, Yuanwei; Yi, Lin; Chen, Jianqing; Weber, Olaf; Boyer, Stephen; Clark, Roger B.; Phillips, Barton; Meahl, Jennifer; Ladouceur, Gaetan; Bi, Cheng; Burke, Michael J.; Cook, James; Verma, Sharad K.; Fan, Jianmei
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003030909	A1	20030417	WO 2002-US30616	20020925

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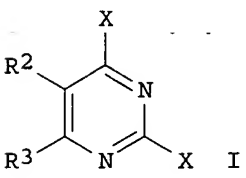
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-324276P P 20010925
US 2002-352509P P 20020131
OTHER SOURCE(S): MARPAT 138:321288
GI



AB The title compds. [I; X = NR1R6, NR4R5, R4, with the proviso that at least one X must be NR1R6; R1 = (un)substituted fused bicyclic unsatd. ring containing 9 or 10 atoms optionally containing 1-4 heteroatoms selected from the group consisting of N, S and O; R2 = H, halo, alkyl, etc.; R3 = H, alkyl, thio; R4 = (un)substituted -Yn-mono-ring group or -Yn-multi-ring group (each ring containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from N, S, and O; n = 0-1; Y = alkylenyl, C(CN); R4 can also be hydrogen or alkyl when R5 is present); R5 = (un)substituted -Yn-mono-ring group or -Yn-multi-ring group (each ring containing 4-18 atoms in the ring and optionally containing 1-4 heteroatoms selected from N, S, and O; n = 0-1; Y = alkylenyl, N:CH, N:CHMe; with the proviso that the multi-ring group cannot be benzimidazolyl); R6 = H, alkyl] which are kinase inhibitors useful in the treatment of cancer and viral infections, were prepared and formulated. Thus, heating 6-aminoquinoline with 2,4-dichloro-5-trifluoromethylpyrimidine (preparation given) in the presence of Na2CO3 in BuOH to 120°C for 3 days afforded I [X = 6-quinolinylamino; R2 = CF3; R3 = H] which showed IC50 of 0.48 μM in in vitro proliferation inhibition assay (HCT 116 human colorectal carcinoma cells).

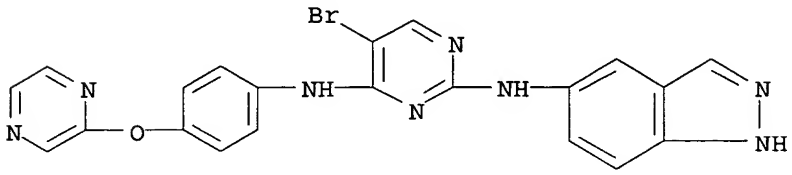
IT **511246-53-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2- and 4-aminopyrimidines as kinase inhibitors in the treatment of cancer)

RN 511246-53-0 HCAPLUS

CN 2,4-Pyrimidinediamine, 5-bromo-N2-1H-indazol-5-yl-N4-[4-(pyrazinyloxy)phenyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

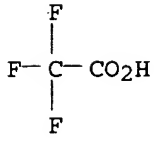
CM 1

CRN 511246-52-9
CMF C21 H15 Br N8 O



CM 2

CRN 76-05-1
CMF C2 H F3 O2



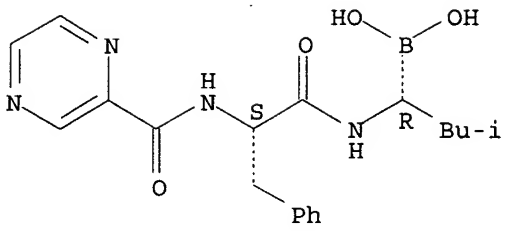
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 8 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:196175 HCAPLUS
DOCUMENT NUMBER: 139:285799
TITLE: Mechanisms of Proteasome Inhibitor PS-341-induced G2-M-Phase Arrest and Apoptosis in Human Non-Small Cell Lung Cancer Cell Lines
AUTHOR(S): Ling, Yi-He; Liebes, Leonard; Jiang, Jian-Dong; Holland, James F.; Elliott, Peter J.; Adams, Julian; Muggia, Franco M.; Perez-Soler, Roman
CORPORATE SOURCE: Department of Oncology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Clinical Cancer Research (2003), 9(3), 1145-1154
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB PS-341 is a novel dipeptide boronic acid proteasome inhibitor with in vitro and in vivo antitumor activity that induces mechanisms of apoptosis by unknown mechanisms. Human non-small cell lung cancer cell lines were used to investigate effects PS-341 on cell proliferation, cell cycle progression, and the induction of apoptosis. PS-341 was 38-360-fold more cytotoxic against H460 cells when compared with the proteasome inhibitors MG-132 and PSI. Differential PS-341 cytotoxic effects were found with respect to P53 function: H322 cells (p53 mutant) were 6-fold less sensitive as compared with H460 cells (p53 wild type); and H358 cells (p53 null) were 1.6-fold more sensitive as compared with H460 cells (p53 wild type). A concentration- and time-dependent cell cycle blockade at G2-M phase was seen for H460 cells without any direct effects on microtubule polymerization or depolymn. PS-341 exposure in H460 cells led to stabilization of p53, induction of p21cip/waf-1 and MDM2 expression, an increase in cyclin B and cyclin A, and the activation of cyclin B and cyclin A **kinases.** MDM2 induction was found only in H460 cells, whereas in H322 and H358 cells, G2-M-phase arrest, p21cip/waf-1 induction, and an increase in cyclin B1 were found. The commitment of G2-M-phase cells to apoptosis was verified by the activation of caspase-3 and cleavage of poly(ADP-ribose) polymerase in drug-free medium. Our data suggest that the PS-341-induced G2-M-phase arrest may be associated with the inhibition of degradation of cell cycle **regulators** and that the up-**regulation** of p21cip/waf-1 expression may be via p53-dependent and/or -independent pathways. The resulting disturbance of cell cycle progression leads either to growth inhibition or to the initiation of apoptotic pathways.

IT **179324-69-7**, PS-341
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanisms of proteasome inhibitor PS-341-induced G2-M-phase arrest and apoptosis in human NSCLC)
RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 9 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:157309 HCAPLUS
DOCUMENT NUMBER: 139:240060
TITLE: Antifibrogenic effects of canrenone, an antialdosteronic drug, on human hepatic stellate cells
AUTHOR(S): Caligiuri, Alessandra; De Franco, Raffaella M. S.; Romanelli, Roberto G.; Gentilini, Alessandra; Meucci, Marta; Failli, Paola; Mazzetti, Luca; Rombouts, Krista; Geerts, Albert; Vanasia, Massimo; Gentilini, Paolo; Marra, Fabio; Pinzani, Massimo
CORPORATE SOURCE: Dipartimento di Medicina Interna, Universita di Firenze, Florence, Italy
SOURCE: Gastroenterology (2003), 124(2), 504-520
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English

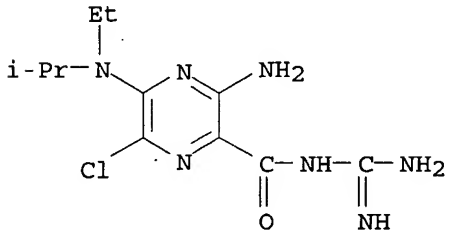
AB Background & Aims: Several lines of evidence indicate that aldosterone antagonists may exert direct antifibrogenic effects. The aim of this study was to evaluate the possible direct antifibrogenic effects of canrenone, the active metabolite of spironolactone, in activated human hepatic stellate cells. Methods: The effects of canrenone were assessed on platelet-derived growth factor-induced mitogenic and chemotactic effects and the increased de novo synthesis of different extracellular matrix components induced by transforming growth factor-β1. Results: Canrenone dose-dependently reduced platelet-derived growth factor-induced cell proliferation and motility. This effect was not associated with either changes in the phosphorylation of platelet-derived growth factor receptor and phospholipase C γ or in the activation of the Ras/extracellular signal-**regulated kinase** pathway, whereas it was accompanied by a dose-dependent inhibition of platelet-derived growth factor-induced phosphatidylinositol 3-**kinase** activity. In addition, canrenone inhibited the activity of the Na+/H+ exchanger 1 induced by platelet-derived growth factor. The effect of canrenone on Na+/H+ exchanger 1 activity was reproduced by phosphatidylinositol 3-**kinase** inhibitors, thus supporting an inhibitory action of canrenone on phosphatidylinositol 3-**kinase** activity. To further address this possibility, the action of canrenone was compared with that of 2 established Na+/H+ exchanger 1 inhibitors: ethylisopropylamiloride and cariporide. Whereas ethylisopropylamiloride was able to inhibit platelet-derived growth factor-induced phosphatidylinositol 3-**kinase** activity, cariporide was without any effect. Both compds. reproduced the effects of canrenone on platelet-derived growth factor-induced mitogenesis and chemotaxis. Finally, canrenone was able to reduce transforming growth factor-β1-induced de novo synthesis of procollagen type I/IV and fibronectin and thrombin-induced hepatic

stellate cell contraction. Conclusions: These results indicate that canrenone may be active as an antifibrogenic drug.

IT **142243-02-5**, Extracellular signal-**regulated kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (antifibrogenic effects of canrenone, an antialdosteronic drug, on human hepatic stellate cells)
RN 142243-02-5 HCAPLUS
CN Kinase (phosphorylating), mitogen-activated protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **1154-25-2**, EIPA
RL: BSU (Biological study, unclassified); BIOL (Biological study) (comparison standard; antifibrogenic effects of canrenone, an antialdosteronic drug, on human hepatic stellate cells)
RN 1154-25-2 HCAPLUS
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[ethyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 10 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:964481 HCAPLUS
DOCUMENT NUMBER: 138:20458
TITLE: Regulation of expression of transgenes delivered by adeno-associated virus vectors using inhibitors of proteasome function
INVENTOR(S): Hirsch, Raphael; Jennings, Kristi J.
PATENT ASSIGNEE(S): Children's Hospital Research Foundation, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002101012	A2	20021219	WO 2002-US18194	20020610
WO 2002101012	A3	20031030		
WO 2002101012	C2	20031218		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003003583 A1 20030102 US 2002-166536 20020610

PRIORITY APPLN. INFO.: US 2001-297125P P 20010608

AB The present invention provides for methods regulating the expression of therapeutic genes delivered by adeno-associated virus (AAV) vectors both in vitro and in vivo. Specifically, the present invention provides for methods of using adeno-associated virus for transduction of a target gene in a variety of tissues wherein the expression of the transgene is regulated by administration of a proteasome inhibitor. Treatment of animal cells with proteasome inhibitors has been shown to increase the nuclear concentration of AAV particles and genomes. As an example, a therapeutic gene can be delivered in vivo by an adeno-associated virus to a tissue that is not normally transduced by adeno-associated virus. The host would then be administered a proteasome inhibitor in order to induce expression of the therapeutic gene. Hence, the proteasome inhibitor would be administered only when gene expression is desired. Human synoviocytes were transformed with an adeno-associated virus carrying a mouse interleukin 10 gene. Incubation of these cells with the proteasome inhibitor zLLL increased level of expression of the gene in a dose-dependent manner. The effect was transient although a long-term effect was predicted. The induction could be repeated by re-exposure to zLLL. In expts. with human synoviocytes and the mouse interleukin 4 gene, a 250-fold increase in the interleukin mRNA was seen upon induction with zLLL.

IT **9002-06-6**, Thymidine **kinase 9013-08-5**, PEP carboxykinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(promoter of gene for, expression of therapeutic gene from adenovirus vector using; **regulation** of expression of transgenes delivered by adeno-associated virus vectors using inhibitors of proteasome function)

RN 9002-06-6 HCAPLUS

CN Kinase (phosphorylating), thymidine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 9013-08-5 HCAPLUS

CN Carboxykinase, phosphoenolpyruvate (guanosine triphosphate) (9CI) (CA INDEX NAME)

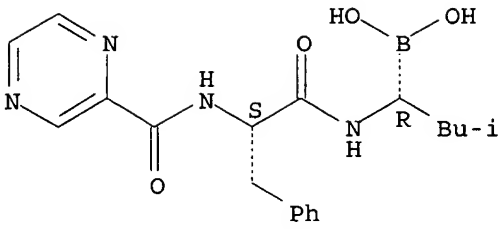
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **179324-69-7**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of expression of transgenes delivered by adeno-associated virus vectors using inhibitors of proteasome function)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

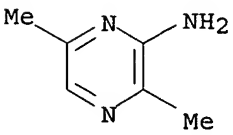
Absolute stereochemistry.



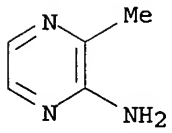
L23 ANSWER 11 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:954429 HCAPLUS
DOCUMENT NUMBER: 138:147177
TITLE: Aloisines, a New Family of CDK/GSK-3 Inhibitors. SAR Study, Crystal Structure in Complex with CDK2, Enzyme Selectivity, and Cellular Effects
AUTHOR(S): Mettey, Yvette; Gompel, Marie; Thomas, Virginie; Garnier, Matthieu; Leost, Maryse; Ceballos-Picot, Irene; Noble, Martin; Endicott, Jane; Vierfond, Jean-Michel; Meijer, Laurent
CORPORATE SOURCE: Faculte de Medecine et de Pharmacie, Poitiers, 86005, Fr.
SOURCE: Journal of Medicinal Chemistry (2003), 46(2), 222-236
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:147177

AB Cyclin-dependent **kinases** (CDKs) **regulate** the cell cycle, apoptosis, neuronal functions, transcription, and exocytosis. The observation of CDK deregulations in various pathol. situations suggests that CDK inhibitors may have a therapeutic value. In this article, we report on the identification of 6-phenyl[5H]pyrrolo[2,3-b]pyrazines (aloisines) as a novel potent CDK inhibitory scaffold. A selectivity study performed on 26 **kinases** shows that aloisine A is highly selective for CDK1/cyclin B, CDK2/cyclin A-E, CDK5/p25, and GSK-3α/β; the two latter enzymes have been implicated in Alzheimer's disease. Kinetic studies, as well as the resolution of a CDK2-aloisine cocrystal structure, demonstrate that aloisines act by competitive inhibition of ATP binding to the catalytic subunit of the **kinase.** As observed with all inhibitors reported so far, aloisine interacts with the ATP-binding pocket through two hydrogen bonds with backbone nitrogen and oxygen atoms of Leu 83. Aloisine inhibits cell proliferation by arresting cells in both G1 and G2.

IT **13134-38-8 19838-08-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and structure activity relationships of aloisines as CDK/GSK-3 inhibitors.)
RN 13134-38-8 HCAPLUS
CN Pyrazinamine, 3,6-dimethyl- (9CI) (CA INDEX NAME)



RN 19838-08-5 HCAPLUS
CN Pyrazinamine, 3-methyl- (9CI) (CA INDEX NAME)



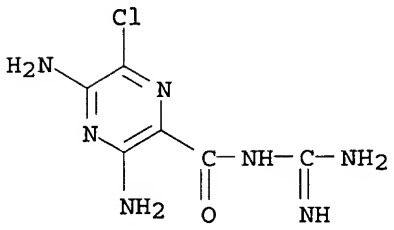
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 12 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:896077 HCAPLUS
DOCUMENT NUMBER: 138:165615
TITLE: Protein Kinase C Isoform Antagonism Controls BNaC2 (ASIC1) Function
AUTHOR(S): Berdiev, Bakhrom K.; Xia, Jiazeng; Jovov, Biljana; Markert, James M.; Mapstone, Timothy B.; Gillespie, G. Yancey; Fuller, Catherine M.; Bubien, James K.; Benos, Dale J.
CORPORATE SOURCE: Departments of Physiology and Biophysics, University of Birmingham, Birmingham, AL, 35294, USA
SOURCE: Journal of Biological Chemistry (**2002**), 277(48), 45734-45740
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We explored the involvement of protein **kinase** C (PKC) and its isoforms in the **regulation** of BNaC2. Reverse transcriptase PCR evaluation of PKC isoform expression at the level of mRNA revealed the presence of α and ε/ε' in all glioma cell lines analyzed; most, but not all cell lines expressed δ and ζ. No messages were found for the βI and βII isotypes of PKC in the tumor cells. Normal astrocytes expressed β but not γ. The essential features of these results were confirmed at the protein level by Western anal. This disproportionate pattern of PKC isoform expression in glioma cell lines was further echoed in the functional effects of these PKC isoforms on BNaC2 activity in bilayers. PKC holoenzyme or the combination of PKCβI and PKCβII isoforms inhibited BNaC2. Neither PKCε nor PKCζ or their combination had any effect on BNaC2 activity in bilayers. The inhibitory effect of the PKCβI and PKCβII mixture on BNaC2 activity was abolished by a 5-fold excess of a PKCε and PKCζ combination. PKC holoenzymes, PKCβI, PKCβII, PKCδ, PKCε, and PKCζ phosphorylated BNaC2 in vitro. In patch clamp expts., the combination of PKCβI and PKCβII inhibited the basally activated inward Na+ conductance. The variable expression of the PKC isotypes and their functional antagonism in **regulating** BNaC2 activity support the idea that the participation of multiple PKC isotypes contributes to the overall activity of BNaC2.

IT **2609-46-3**, Amiloride
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(protein kinase C isoforms can activate amiloride-senstive sodium channel in glioma cells)
RN 2609-46-3 HCAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



IT **141436-78-4**, Protein **kinase** C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(βI, βII, δ, ε and ζ; protein
kinase C isoforms can **regulate** amiloride-senstive
sodium channel in glioma cells)
RN 141436-78-4 HCAPLUS
CN Kinase (phosphorylating), protein, cPKC (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 13 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:859198 HCAPLUS
DOCUMENT NUMBER: 138:395597
TITLE: Molecular sequelae of proteasome inhibition in human multiple myeloma cells
AUTHOR(S): Mitsiades, Nicholas; Mitsiades, Constantine S.; Poulaki, Vassiliki; Chauhan, Dharminder; Fanourakis, Galinos; Gu, Xuesong; Bailey, Charles; Joseph, Marie; Libermann, Towia A.; Treon, Steven P.; Munshi, Nikhil C.; Richardson, Paul G.; Hideshima, Teru; Anderson, Kenneth C.
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**2002**), 99(22), 14374-14379
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The proteasome inhibitor PS-341 inhibits IκB degradation, prevents NF-κB activation, and induces apoptosis in several types of cancer cells, including chemoresistant multiple myeloma (MM) cells. PS-341 has marked clin. activity even in the setting of relapsed refractory MM. However, PS-341-induced apoptotic cascade(s) are not yet fully defined. By using gene expression profiling, we characterized the mol. sequelae of PS-341 treatment in MM cells and further focused on mol. pathways responsible for the anticancer actions of this promising agent. The transcriptional profile of PS-341-treated cells involved down-**regulation** of growth/survival signaling pathways, and up-**regulation** of mols. implicated in proapoptotic cascades (which are both consistent with the proapoptotic effect of proteasome inhibition), as

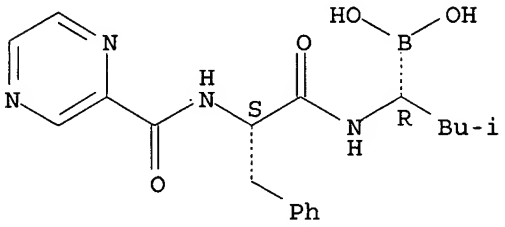
well as up-**regulation** of heat-shock proteins and ubiquitin/proteasome pathway members (which can correspond to stress responses against proteasome inhibition). Further studies on these pathways showed that PS-341 decreases the levels of several antiapoptotic proteins and triggers a dual apoptotic pathway of mitochondrial cytochrome c release and caspase-9 activation, as well as activation of Jun **kinase** and a Fas/caspase-8-dependent apoptotic pathway [which is inhibited by a dominant neg. (decoy) Fas construct]. Stimulation with IGF-1, as well as overexpression of Bcl-2 or constitutively active Akt in MM cells also modestly attenuates PS-341-induced cell death, whereas inhibitors of the BH3 domain of Bcl-2 family members or the heat-shock protein 90 enhance tumor cell sensitivity to proteasome inhibition. These data provide both insight into the mol. mechanisms of antitumor activity of PS-341 and the rationale for future clin. trials of PS-341, in combination with conventional and novel therapies, to improve patient outcome in MM.

IT **179324-69-7**, PS 341
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mol. sequelae of proteasome inhibition with PS-341 in human multiple myeloma cells)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 14 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:544866 HCAPLUS

DOCUMENT NUMBER: 138:100560

TITLE: Na+/H+ exchanger blockade inhibits enterocyte inflammatory response and protects against colitis

AUTHOR(S): Nemeth, Zoltan H.; Deitch, Edwin A.; Szabo, Csaba; Mabley, Jon G.; Pacher, Pal; Fekete, Zoltan; Hauser, Carl J.; Hasko, Gyorgy

CORPORATE SOURCE: Department of Surgery, New Jersey Medical School, University of Medicine and Dentistry of New Jersey, Newark, NJ, 07103, USA

SOURCE: American Journal of Physiology (**2002**), 283(1, Pt. 1), G122-G132
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

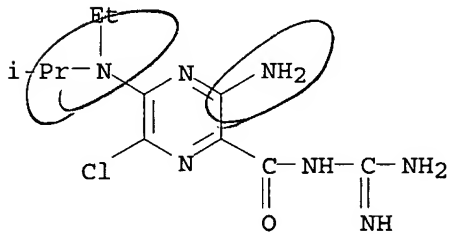
LANGUAGE: English

AB Na+/H+ exchangers (NHEs) are integral transmembrane proteins found in all mammalian cells. There is substantial evidence indicating that NHEs **regulate** inflammatory processes. Because intestinal epithelial

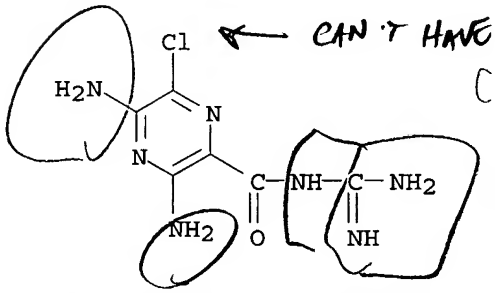
cells express a variety of NHEs, the authors tested the possibility that NHEs are also involved in **regulation** of the epithelial cell inflammatory response. In addition, since the epithelial inflammatory response is an important contributor to mucosal inflammation in inflammatory bowel disease (IBD), the authors examined the role of NHEs in the **modulation** of disease activity in a mouse model of IBD. In human gut epithelial cells, NHE inhibition using a variety of agents, including amiloride, 5-(N-methyl-N-isobutyl)amiloride, 5-(N-ethyl-N-isopropyl)amiloride, harmaline, clonidine, and cimetidine, suppressed interleukin-8 (IL-8) production The inhibitory effect of NHE inhibition on IL-8 was associated with a decrease in IL-8 mRNA accumulation. NHE inhibition suppressed both activation of the p42/p44 mitogen-activated protein **kinase** and nuclear factor-κB. Finally, NHE inhibition ameliorated the course of IBD in dextran sulfate-treated mice. The authors' data demonstrate that inhibition of NHEs may be an approach worthy of pursuing for the treatment of IBD.

IT **1154-25-2**, 5-(N-Ethyl-N-isopropyl)amiloride **2609-46-3**, Amiloride **96861-65-3**, 5-(N-Methyl-N-isobutyl)amiloride
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Na+/H+ exchanger blockade inhibits enterocyte inflammatory response)

RN 1154-25-2 HCAPLUS
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[ethyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)

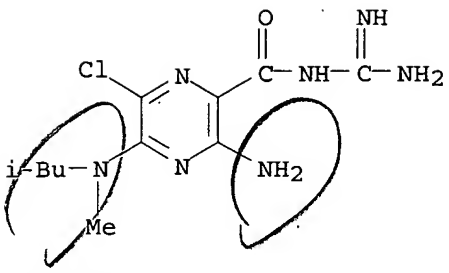


← CAN'T HAVE THIS CHLORO (MUST BE H)

Cl

R_1 OR R_2 CAN'T BE THIS

RN 96861-65-3 HCAPLUS
CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[methyl(2-methylpropyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 15 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:543210 HCAPLUS
DOCUMENT NUMBER: 137:216294
TITLE: Neurotensin- and EGF-induced metabolic activation of colon carcinoma cells is diminished by dietary flavonoid cyanidin but not by its glycosides
AUTHOR(S): Briviba, Karlis; Abrahamse, S. Leo; Pool-Zobel, Beatrice L.; Rechkemmer, Gerhard
CORPORATE SOURCE: Institute for Nutritional Physiology, Federal Research Center for Nutrition, Karlsruhe, D-76131, Germany
SOURCE: Nutrition and Cancer (**2001**), 41(1&2), 172-179
CODEN: NUCADQ; ISSN: 0163-5581
PUBLISHER: Lawrence Erlbaum Associates, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

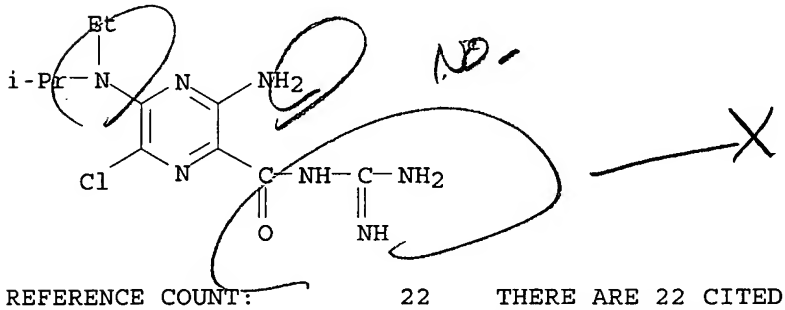
AB Dietary polyphenols, including anthocyanidins and their glycosides anthocyanins, are suggested to be involved in the protective effects of fruits and vegetables against cancer. Very few data are available concerning the effects of anthocyanidins/anthocyanins on cellular processes induced by growth factors such as neurotensin and epidermal growth factor (EGF), which are implicated in the pathophysiol. of colon cancer. Here, we show that neurotensin and EGF caused an increase in the extracellular acidification rate, which could reflect the activity of cellular metabolism, in the human carcinoma cell line HT29 clone 19A. Neurotensin and EGF also caused a strong rise in the intracellular Ca2+ concentration, induced phosphorylation of extracellular signal-**regulated kinases** (ERK1 and ERK2), and stimulated growth of human carcinoma cells. Cyanidin (10 μM), but not its glycosides cyanin and idaein, was able to inhibit the neurotensin- and EGF-induced increased rate of extracellular acidification. In contrast to N-ethyl-N-iso-Pr amiloride, an inhibitor of Na+/H+ exchange, cyanidin did not alter the rate of intracellular pH recovery of cells loaded by NH3/NH4+, indicating that cyanidin inhibits cellular metabolism, rather than directly altering Na+/H+ exchange. Cyanidin, but not cyanin and idaein, was able to inhibit an increase in intracellular Ca2+ concentration induced by neurotensin. Neurotensin- and EGF-induced phosphorylation of ERKS was not affected by cyanidin, cyanin, and idaein at ≤100 μM. Only cyanidin (100 μM), but not cyanin and idaein, was able to inhibit cellular growth induced by EGF. Thus these findings suggest that a dietary polyphenol cyanidin, but not its glyco sides, is a potent inhibitor of mitogen-induced metabolic activity, increase in free intracellular Ca2+, and cellular growth of cultured colon carcinoma cells.

IT **1154-25-2**, EIPA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(neurotensin- and EGF-induced metabolic activation of colon carcinoma

cells is diminished by dietary flavonoid cyanidin but not by its glycosides)

RN 1154-25-2 HCAPLUS

CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[ethyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 16 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:449673 HCAPLUS

DOCUMENT NUMBER: 137:20389

TITLE: Preparation of indenopyrazolone semicarbazides as cyclin dependent kinase inhibitors.

INVENTOR(S): Carini, David J.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

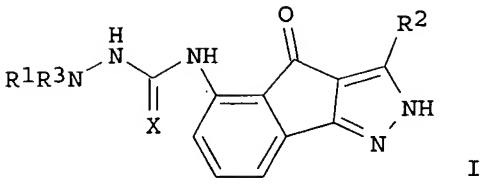
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002046182	A1	20020613	WO 2001-US46904	20011207 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2430376	AA	20020613	CA 2001-2430376	20011207 <--
AU 2002028849	A5	20020618	AU 2002-28849	20011207 <--
US 2002091127	A1	20020711	US 2001-10979	20011207
US 6849631	B2	20050201		
EP 1351956	A1	20031015	EP 2001-989969	20011207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004538247	T2	20041224	JP 2002-547920	20011207

PRIORITY APPLN. INFO.: US 2000-254116P P 20001208
WO 2001-US46904 W 20011207

OTHER SOURCE(S): MARPAT 137:20389

GI



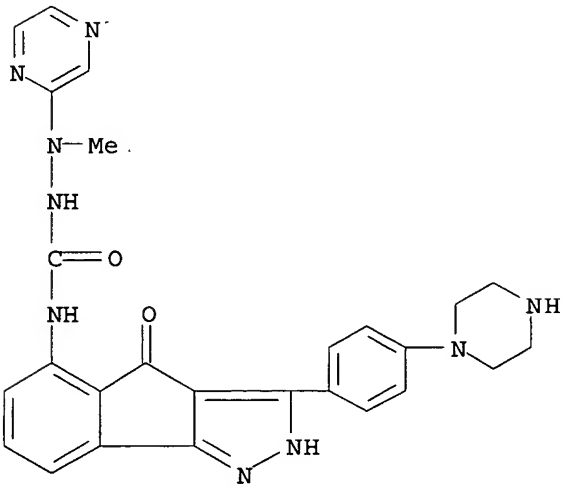
I

AB Title compds. [I; X = O, S; R1 = (substituted) carbocyclyl, heterocyclyl; R2 = H, (substituted) alkyl, alkenyl alkynyl, carbocyclyl, heterocyclyl; R3 = H, alkyl, cycloalkyl, cycloalkylalkyl; with provisos], were prepared as cdk inhibitors (no data). Thus, 3-(4-piperazinophenyl)-5-[[N-methyl-N-(2-pyridinyl)amino]carbamoylamino]indeno[1,2-c]pyrazol-4-1 was prepared in several steps starting from 4-piperazinoacetophenone.

IT **435337-22-7P 435337-30-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of indenopyrazolone semicarbazides as cyclin dependent kinase inhibitors)

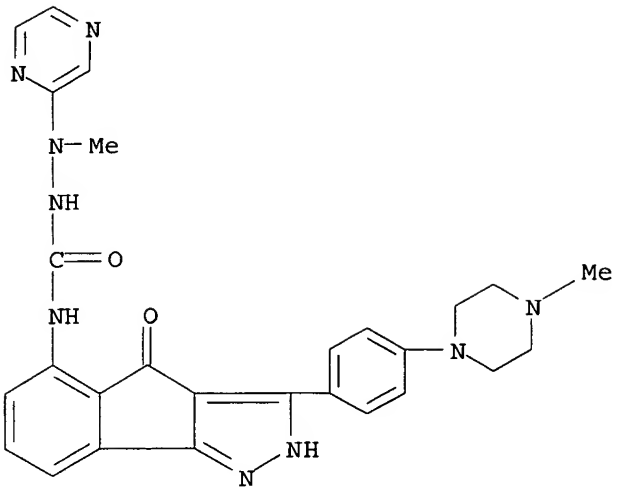
RN 435337-22-7 HCAPLUS

CN Hydrazinecarboxamide, N-[2,4-dihydro-4-oxo-3-[4-(1-piperazinyl)phenyl]indeno[1,2-c]pyrazol-5-yl]-2-methyl-2-pyrazinyl- (9CI) (CA INDEX NAME)

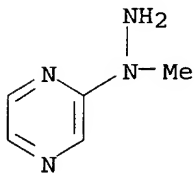


RN 435337-30-7 HCAPLUS

CN Hydrazinecarboxamide, N-[2,4-dihydro-3-[4-(4-methyl-1-piperazinyl)phenyl]-4-oxoindeno[1,2-c]pyrazol-5-yl]-2-methyl-2-pyrazinyl- (9CI) (CA INDEX NAME)



IT **76319-95-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of indenopyrazolone semicarbazides as cyclin dependent kinase inhibitors)
RN 76319-95-4 HCAPLUS
CN Pyrazine, (1-methylhydrazino)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 17 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:371242 HCAPLUS
DOCUMENT NUMBER: 137:304403
TITLE: NF-κB as a therapeutic target in multiple myeloma
AUTHOR(S): Hideshima, Teru; Chauhan, Dharminder; Richardson, Paul; Mitsiades, Constantine; Mitsiades, Nicholas; Hayashi, Toshiaki; Munshi, Nikhil; Dang, Lenny; Castro, Alfredo; Palombella, Vito; Adams, Julian; Anderson, Kenneth C.
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (**2002**), 277(19), 16639-16647
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have shown that thalidomide (Thal) and its immunomodulatory derivs.

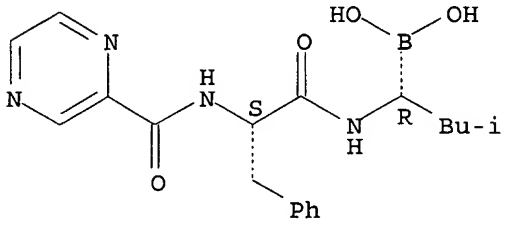
(IMiDs), proteasome inhibitor PS-341, and As2O3 act directly on multiple myeloma (MM) cells and in the bone marrow (BM) milieu to overcome drug resistance. Although Thal/IMiDs, PS-341, and As2O3 inhibit nuclear factor (NF)-κB activation, they also have multiple and varied other actions. In this study, we therefore specifically address the role of NF-κB blockade in mediating anti-MM activity. To characterize the effect of specific NF-κB blockade on MM cell growth and survival in vitro, we used an IκB **kinase** (IKK) inhibitor (PS-1145). Our studies demonstrate that PS-1145 and PS-341 block TNFα-induced NF-κB activation in a dose- and time-dependent fashion in MM cells through inhibition of IκBα phosphorylation and degradation of IκBα, resp. Dexamethasone (Dex), which up- **regulates** IκBα protein, enhances blockade of NF-κB activation by PS-1145. Moreover, PS-1145 blocks the protective effect of IL-6 against Dex-induced apoptosis. TNFα-induced intracellular adhesion mol. (ICAM)-1 expression on both RPMI8226 and MM.1S cells is also inhibited by PS-1145. Moreover, PS-1145 inhibits both IL-6 secretion from BMSCs triggered by MM cell adhesion and proliferation of MM cells adherent to BMSCs. However, in contrast to PS-341, PS-1145 only partially (20-50%) inhibits MM cell proliferation, suggesting that NF-κB blockade cannot account for all of the anti-MM activity of PS-341. Importantly, however, TNFα induces MM cell toxicity in the presence of PS-1145. These studies demonstrate that specific targeting of NF-κB can overcome the growth and survival advantage conferred both by tumor cell binding to BMSCs and cytokine secretion in the BM milieu. Furthermore, they provide the framework for clin. evaluation of novel MM therapies based upon targeting NF-κB.

IT **179324-69-7**, PS-341
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NF-κB as a therapeutic target in multiple myeloma)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 18 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:240758 HCAPLUS
DOCUMENT NUMBER: 136:279477
TITLE: Preparation of pyrazines as **modulators** of vascular endothelial growth factor (VEGF) receptor tyrosine **kinase.**
INVENTOR(S): Kuo, Gee Hong; Connolly, Peter; Prouty, Catherine; Deangelis, Alan; Wang, Aihua; Jolliffe, Linda; Middleton, Steve; Emanuel, Stuart
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA

SOURCE: PCT Int. Appl., 202 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024681	A2	20020328	WO 2001-US29175	20010919 <--
WO 2002024681	A3	20020620		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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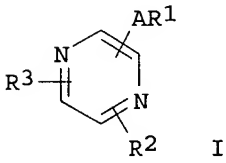
AU 2001094584	A5	20020402	AU 2001-94584	20010919 <--
US 2003060629	A1	20030327	US 2001-955780	20010919
US 6710048	B2	20040323		
EP 1330452	A2	20030730	EP 2001-975243	20010919
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004523474	T2	20040805	JP 2002-529091	20010919

PRIORITY APPLN. INFO.:
US 2000-233968P P 20000920
WO 2001-US29175 W 20010919

OTHER SOURCE(S): MARPAT 136:279477
GI



I

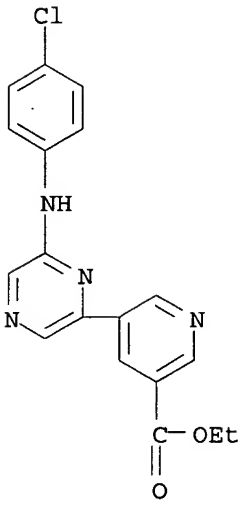
AB The present invention also provides pharmaceutical formulations containing the pyrazine derivs. and methods of use of these formulations as anti-tumor agents and to treat solid-tumor cancers, angiogenesis, diabetic retinopathy, rheumatoid arthritis, endometriosis and psoriasis. Title compds. [I; R1 = (substituted) cycloalkyl, (bi)heterocyclyl, (bi)aryl, (bi)heteroaryl; A = N(R4)(CH2)x, O(CH2)x, S(CH2)x, SO2(CH2)x, SO2N(CH2)x, NSO2(CH2)x, N(R4)CONH(CH2)x, etc.; x = 0-4; R4 = H, alkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, alkenyl, (substituted) aryl, heteroaryl; R2 = (substituted) (bi)heteroaryl; R3 = H, alkyl, alkoxy, alkenyl, alkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxy, aryl, aralkyl, aralkoxy, OH, hydroxyalkyl, halo, cyano, NO2, amino, (hydroxyalkyl)amino, di(hydroxyalkyl)amino, carbamoyl, acyl, acylalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, acylamino, alkylsulfonyl, alkylsulfonylamino, (substituted) arylsulfonylamino], were prepared Thus, a mixture of Et 5-bromonicotinate, bis(tributyltin), Pd(OAc)2, tri-o-tolylphosphine, and

Et3N in MeCN was stirred at 95-100° for 22 h. to give 40% Et 5-trimethylstannylnicotinate. The latter with 2,6-dichloropyrazine, Pd(PPh3)2Cl2, and LiCl were stirred in PhMe at 100° for 23 h to give 60% Et 5-(6-chloropyrazin-2-yl)nicotinate. The latter with 3-chloroaniline, Pd2(dba)3, DPPF, and Cs2CO3 were stirred in dioxane at 110° for 46 h to give Et 5-[6-(3-chlorophenylamino)]pyrazin-2-ylnicotinate. This was converted to 3-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-1-propanol in several steps. The latter inhibited HeLa cell proliferation with IC50 = 4.56 μM.

IT **405939-06-2P 405939-07-3P 405939-08-4P**
405939-09-5P 405939-10-8P 405939-11-9P
405939-12-0P 405939-13-1P 405939-14-2P
405939-15-3P 405939-16-4P 405939-17-5P
405939-18-6P 405939-19-7P 405939-20-0P
405939-21-1P 405939-22-2P 405939-25-5P
405939-26-6P 405939-27-7P 405939-31-3P
405939-33-5P 405939-34-6P 405939-35-7P
405939-36-8P 405939-37-9P 405939-38-0P
405939-42-6P 405939-43-7P 405939-44-8P
405939-45-9P 405939-46-0P 405939-47-1P
405939-53-9P 405939-56-2P 405939-57-3P
405939-64-2P 405939-65-3P 405939-66-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of)

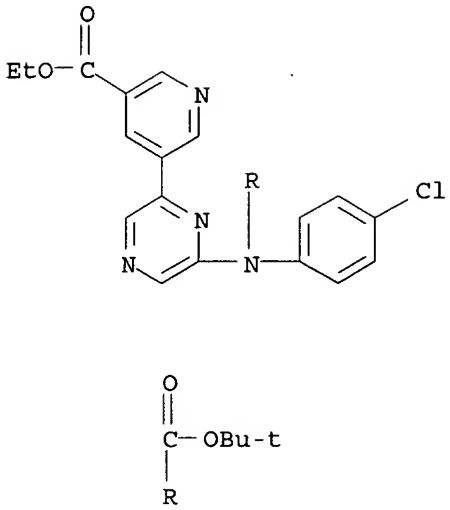
RN 405939-06-2 HCAPLUS

CN 3-Pyridinecarboxylic acid, 5-[6-[(4-chlorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

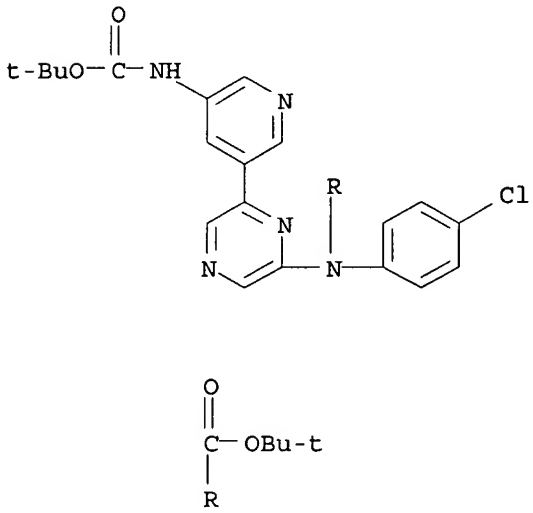


RN 405939-07-3 HCAPLUS

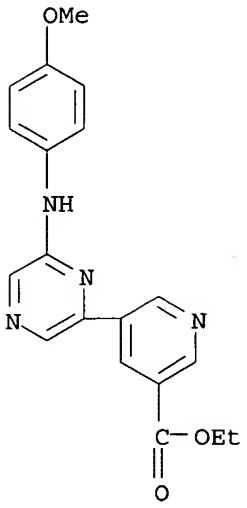
CN 3-Pyridinecarboxylic acid, 5-[6-[(4-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



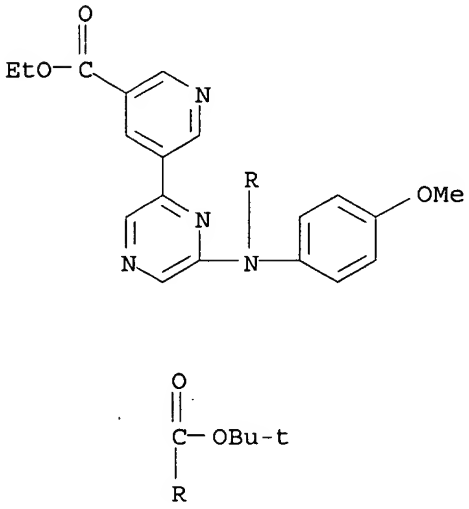
RN 405939-08-4 HCAPLUS
CN Carbamic acid, [5-[6-[(4-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



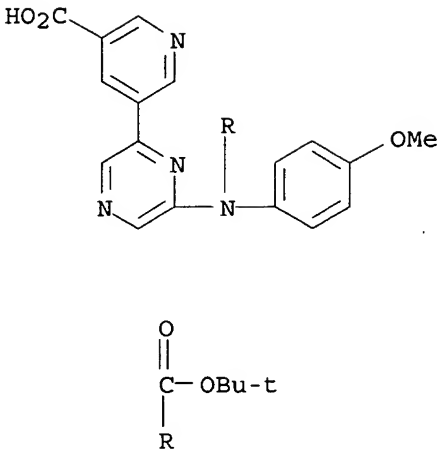
RN 405939-09-5 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(4-methoxyphenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



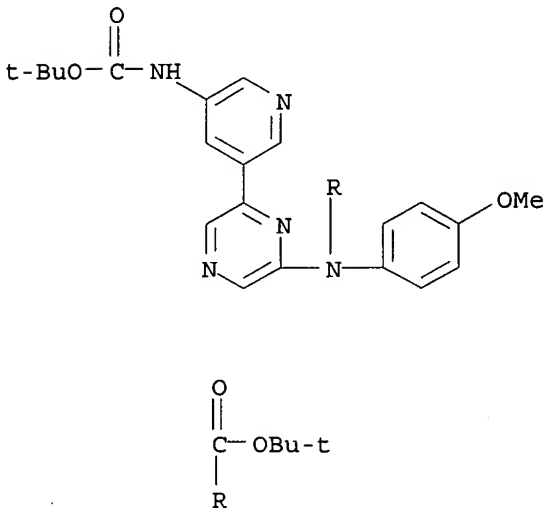
RN 405939-10-8 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](4-methoxyphenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



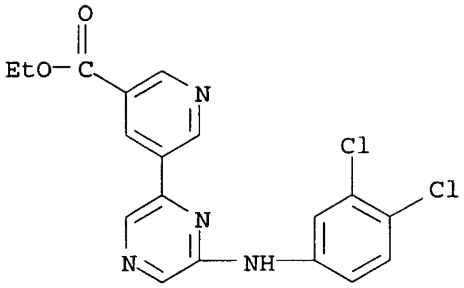
RN 405939-11-9 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](4-methoxyphenyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)



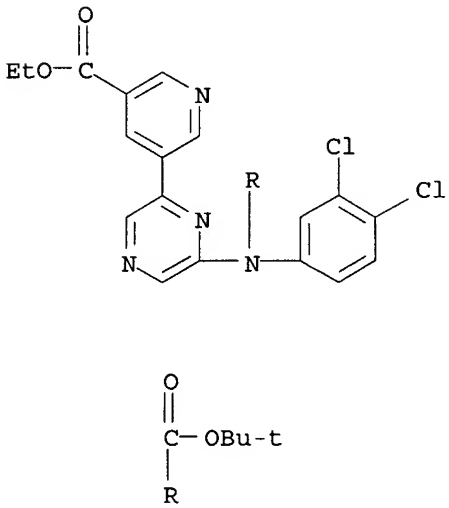
RN 405939-12-0 HCAPLUS
CN Carbamic acid, [6-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl](4-methoxyphenyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



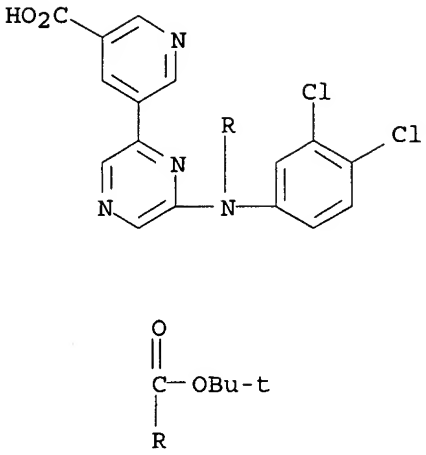
RN 405939-13-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3,4-dichlorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



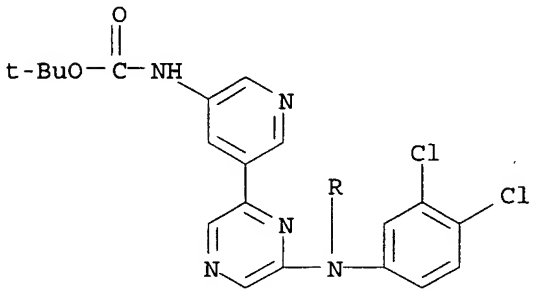
RN 405939-14-2 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3,4-dichlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

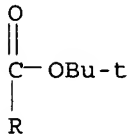


RN 405939-15-3 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3,4-dichlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]- (9CI) (CA INDEX NAME)

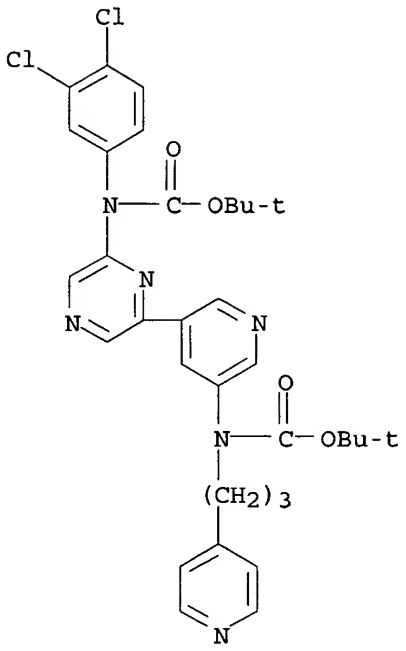


RN 405939-16-4 HCAPLUS
CN Carbamic acid, [5-[6-[(3,4-dichlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

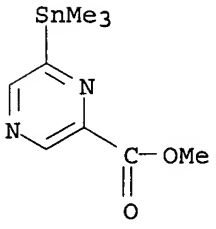




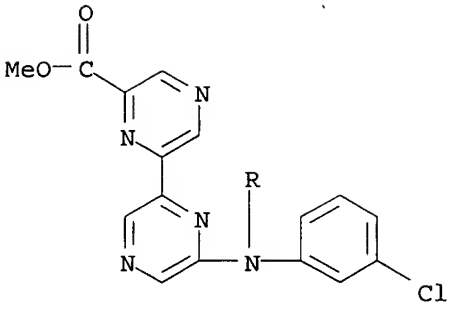
RN 405939-17-5 HCAPLUS
CN Carbamic acid, [5-[6-[(3,4-dichlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][3-(4-pyridinyl)propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

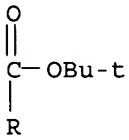


RN 405939-18-6 HCAPLUS
CN Pyrazinecarboxylic acid, 6-(trimethylstannyl)-, methyl ester (9CI) (CA INDEX NAME)

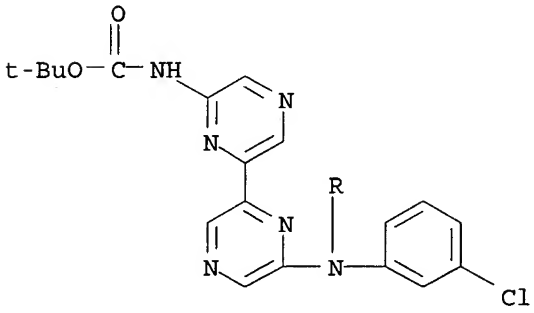


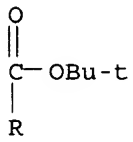
RN 405939-19-7 HCAPLUS
CN [2,2'-Bipyrazine]-6-carboxylic acid, 6'-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)



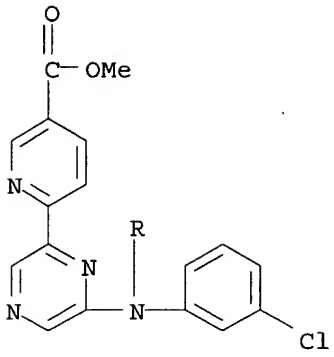


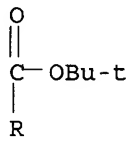
RN 405939-20-0 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6'-[[(1,1-dimethylethoxy)carbonyl]amino][2,2'-bipyrazin]-6-yl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



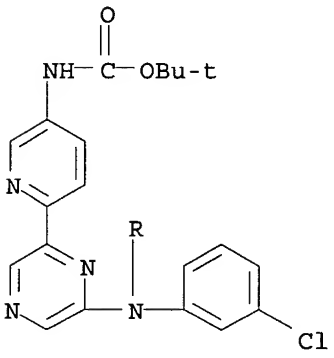


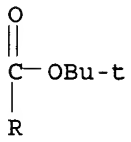
RN 405939-21-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 6-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, methyl ester (9CI) (CA INDEX NAME)



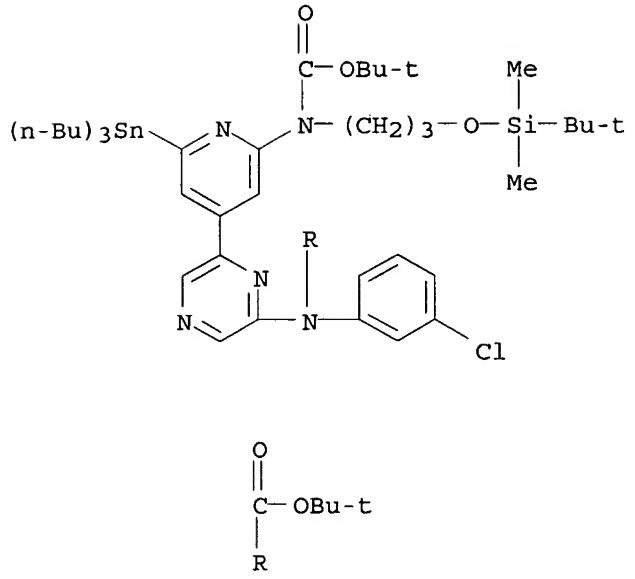


RN 405939-22-2 HCAPLUS
CN Carbamic acid, [6-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

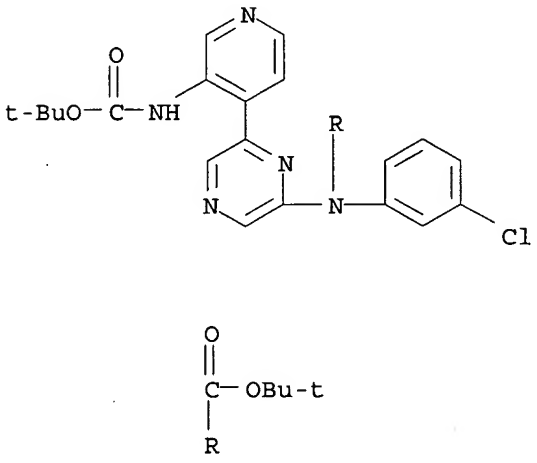




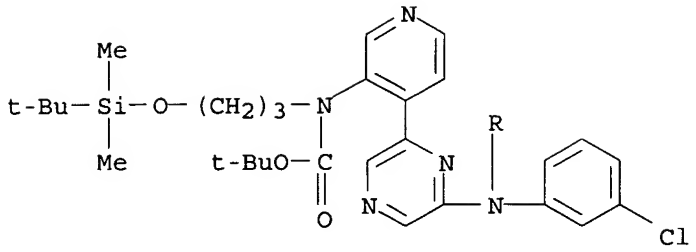
RN 405939-25-5 HCAPLUS
CN Carbamic acid, [4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-6-(tributylstannyl)-2-pyridinyl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

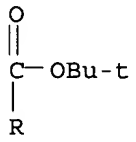


RN 405939-26-6 HCAPLUS
CN Carbamic acid, [4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

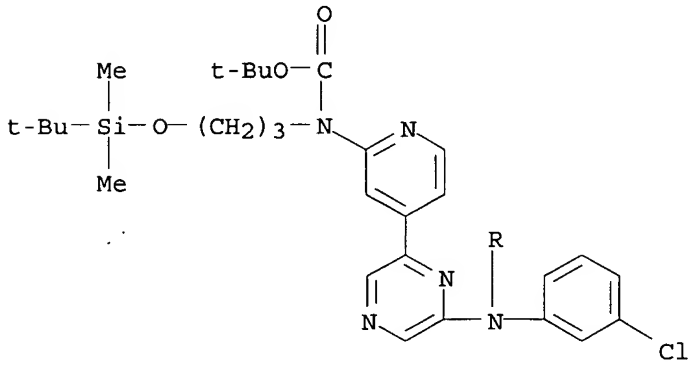


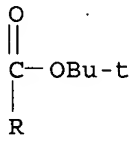
RN 405939-27-7 HCAPLUS
CN Carbamic acid, [4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



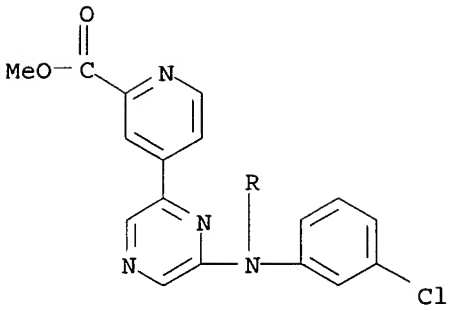


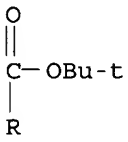
RN 405939-31-3 HCAPLUS
CN Carbamic acid, [4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-2-pyridinyl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



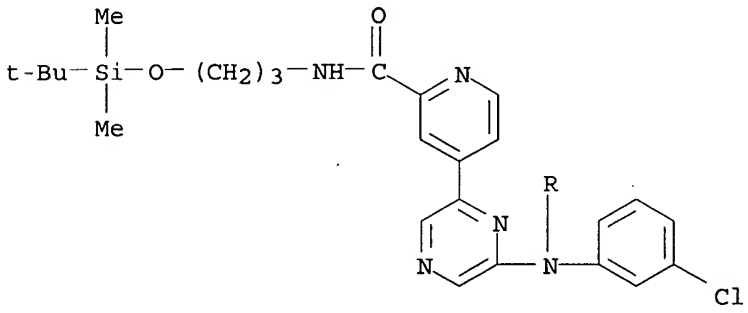


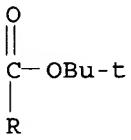
RN 405939-33-5 HCAPLUS
CN 2-Pyridinecarboxylic acid, 4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, methyl ester (9CI) (CA INDEX NAME)



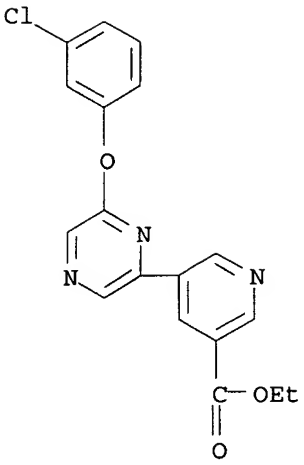


RN 405939-34-6 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6-[2-[[[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]amino]carbonyl]-4-pyridinyl]pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

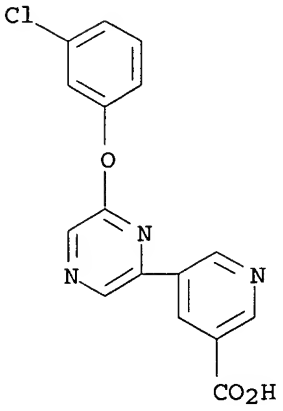




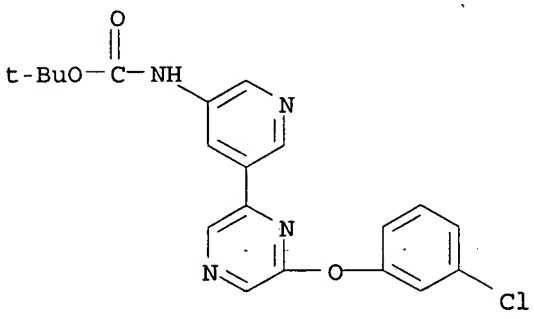
RN 405939-35-7 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-(3-chlorophenoxy)pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



RN 405939-36-8 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-(3-chlorophenoxy)pyrazinyl]- (9CI) (CA INDEX NAME)

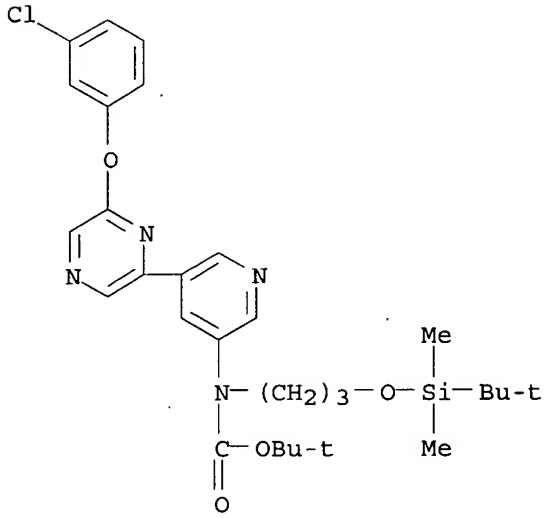


RN 405939-37-9 HCAPLUS
CN Carbamic acid, [5-[6-(3-chlorophenoxy)pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

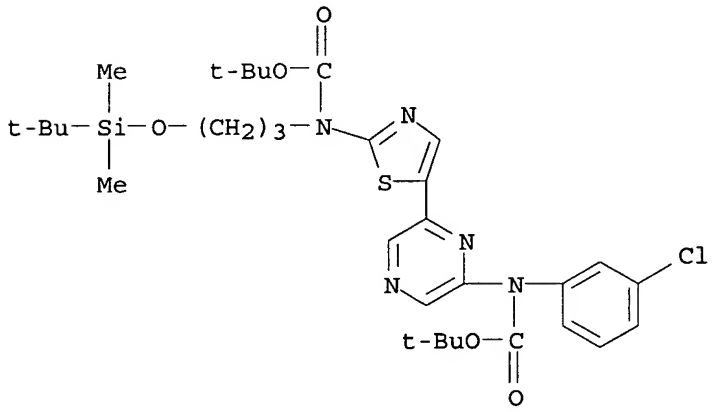


RN 405939-38-0 HCAPLUS

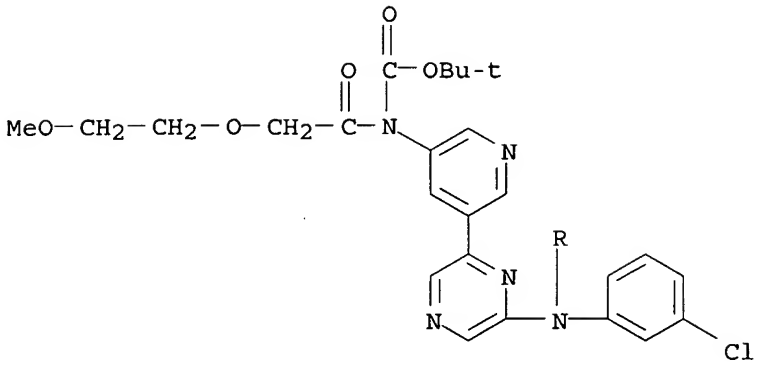
CN Carbamic acid, [5-[6-(3-chlorophenoxy)pyrazinyl]-3-pyridinyl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

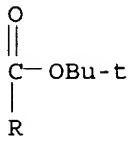


RN 405939-42-6 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-2-thiazolyl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

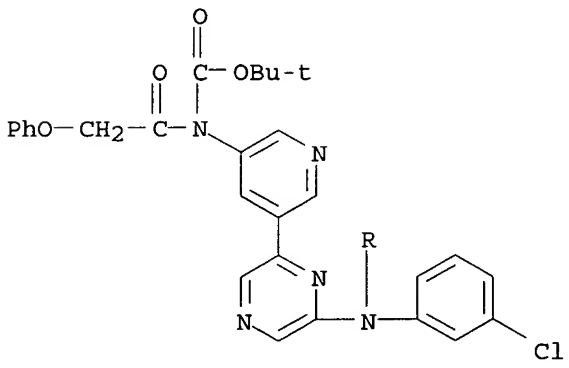


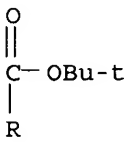
RN 405939-43-7 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][(2-methoxyethoxy)acetyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



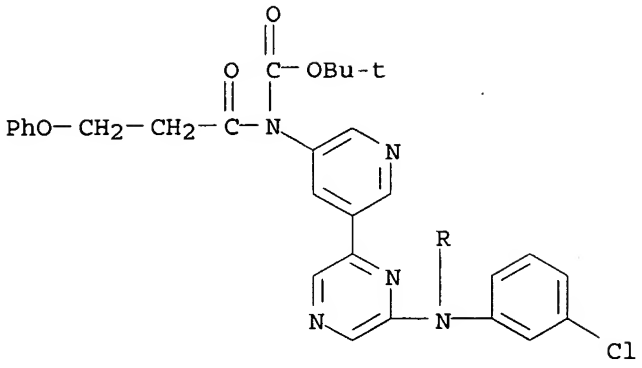


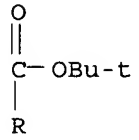
RN 405939-44-8 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl](phenoxyacetyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



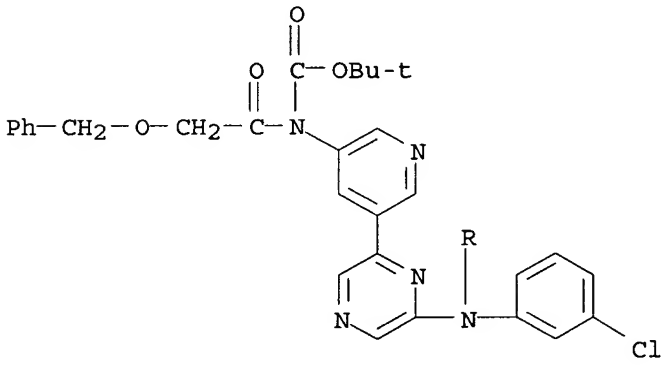


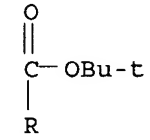
RN 405939-45-9 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl](1-oxo-3-phenoxypropyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



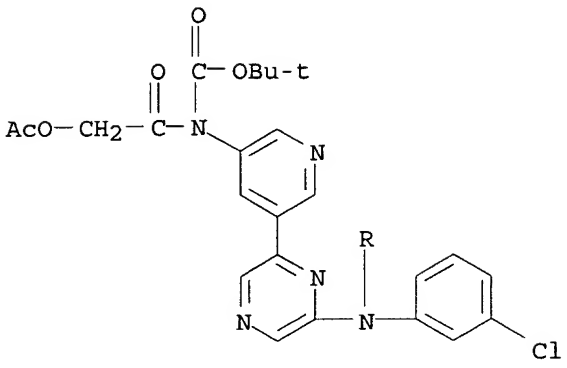


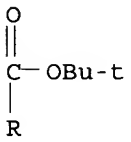
RN 405939-46-0 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][(phenylmethoxy)acetyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



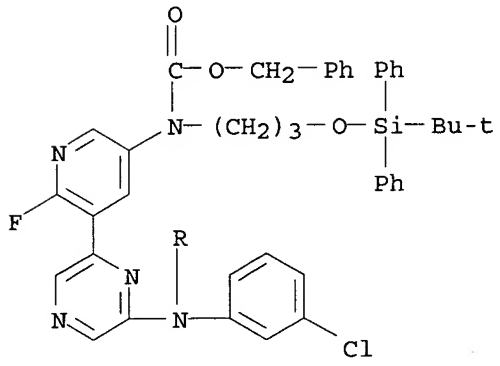


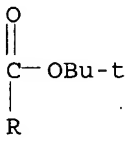
RN 405939-47-1 HCAPLUS
CN Carbamic acid, [(acetyloxy)acetyl][5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



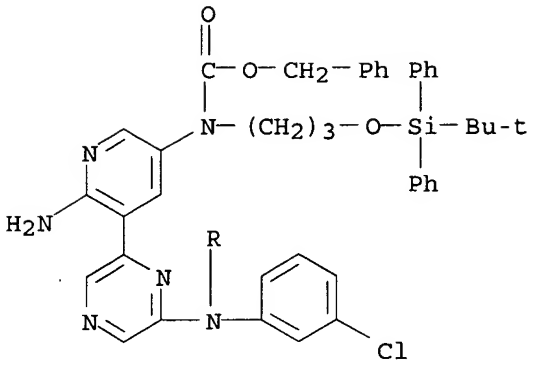


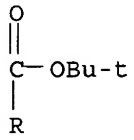
RN 405939-53-9 HCAPLUS
CN Carbamic acid, [5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-6-fluoro-3-pyridinyl][3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



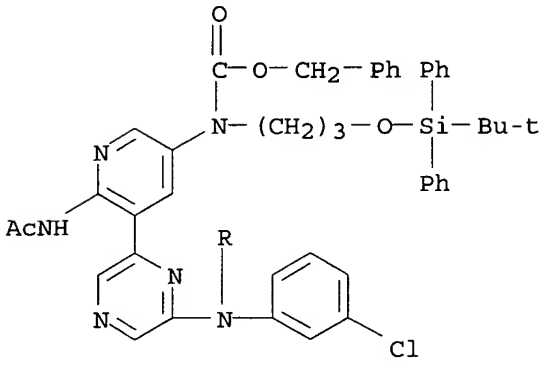


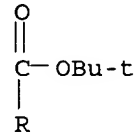
RN 405939-56-2 HCAPLUS
CN Carbamic acid, [6-amino-5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



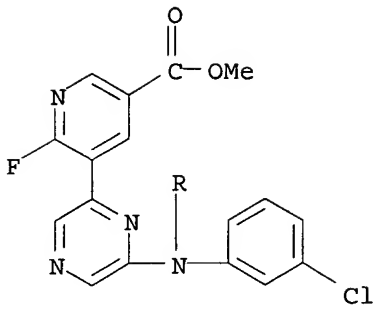


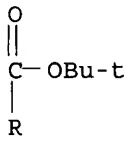
RN 405939-57-3 HCAPLUS
CN Carbamic acid, [6-(acetylamino)-5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]-, phenylmethyl ester (9CI) (CA INDEX NAME)



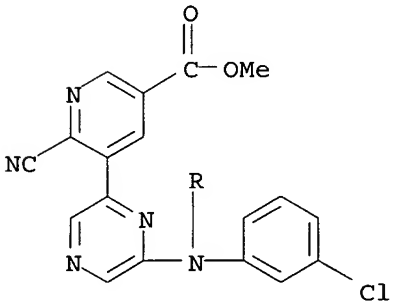


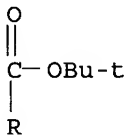
RN 405939-64-2 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-6-fluoro-, methyl ester (9CI) (CA INDEX NAME)



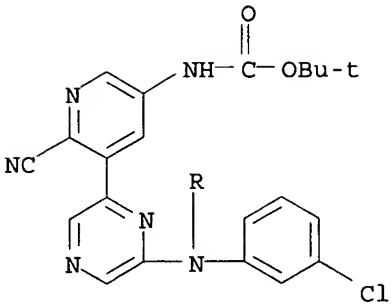


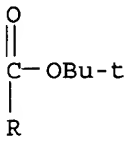
RN 405939-65-3 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-6-cyano-, methyl ester (9CI) (CA INDEX NAME)





RN 405939-66-4 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6-[2-cyano-5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)





IT **405938-58-1P 405938-62-7P 405938-64-9P**
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405938-71-8P 405938-72-9P 405938-73-0P
405938-74-1P 405938-75-2P 405938-76-3P
405938-77-4P 405938-78-5P 405938-79-6P
405938-80-9P 405938-81-0P 405938-82-1P
405938-83-2P 405938-84-3P 405938-85-4P
405938-86-5P 405938-87-6P 405938-88-7P
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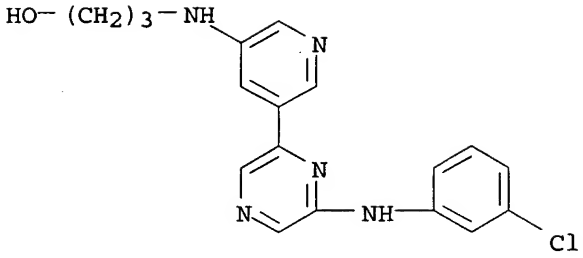
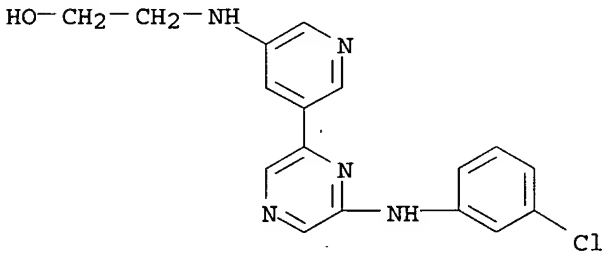
405940-43-4P 405940-44-5P 405940-45-6P
405940-46-7P 405940-47-8P 405940-48-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrazines as **modulators** of vascular endothelial growth factor (VEGF) receptor tyrosine **kinase**)

RN 405938-58-1 HCAPLUS

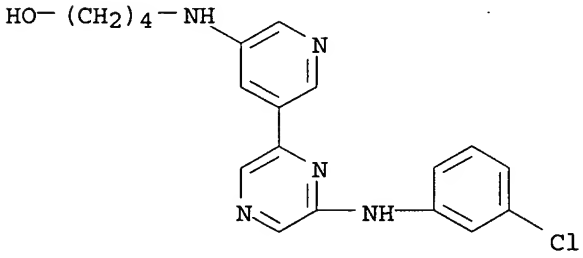
CN 1-Propanol, 3-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-(9CI) (CA INDEX NAME)



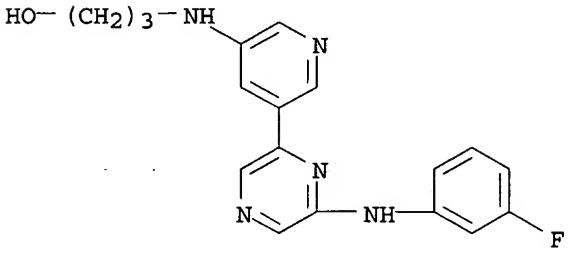
RN 405938-62-7 HCAPLUS
CN Ethanol, 2-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-
(9CI) (CA INDEX NAME)



RN 405938-64-9 HCAPLUS
CN 1-Butanol, 4-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-
(9CI) (CA INDEX NAME)

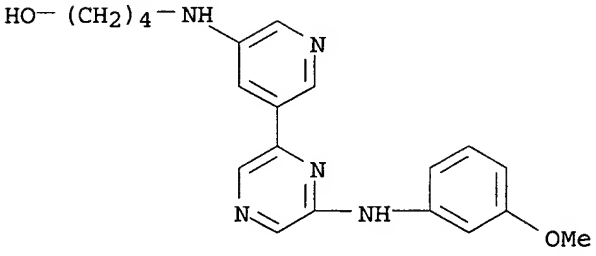


RN 405938-66-1 HCAPLUS
CN 1-Propanol, 3-[[5-[6-[(3-fluorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-
(9CI) (CA INDEX NAME)

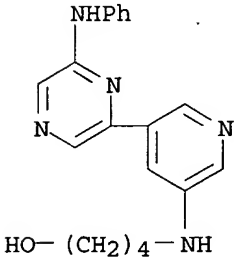


RN 405938-68-3 HCAPLUS

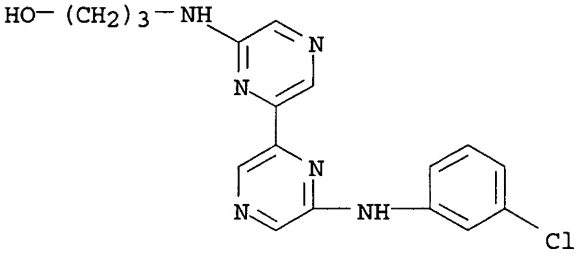
CN 1-Butanol, 4-[[5-[6-[(3-methoxyphenyl)amino]pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



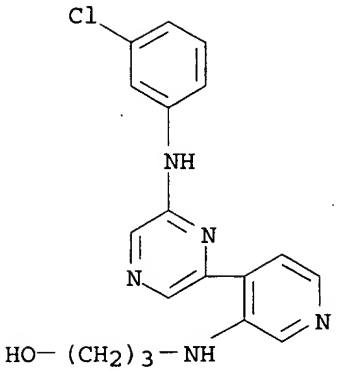
RN 405938-70-7 HCAPLUS
CN 1-Butanol, 4-[[5-[6-(phenylamino)pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



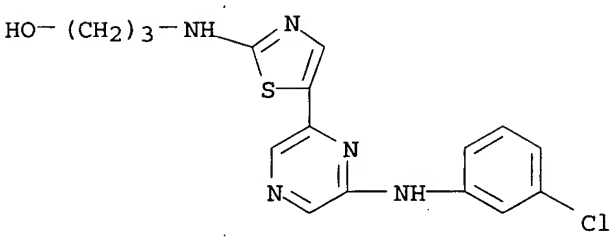
RN 405938-71-8 HCAPLUS
CN 1-Propanol, 3-[[6'-[(3-chlorophenyl)amino][2,2'-bipyrazin]-6-yl]amino]- (9CI) (CA INDEX NAME)



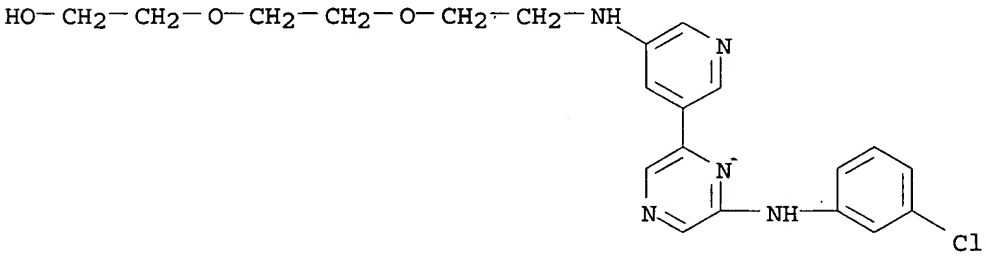
RN 405938-72-9 HCAPLUS
CN 1-Propanol, 3-[[4-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



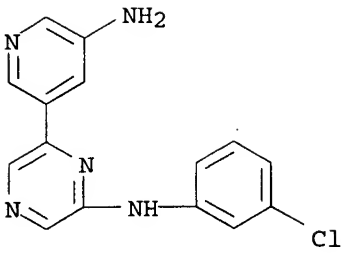
RN 405938-73-0 HCAPLUS
CN 1-Propanol, 3-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-2-thiazolyl]amino]- (9CI) (CA INDEX NAME)



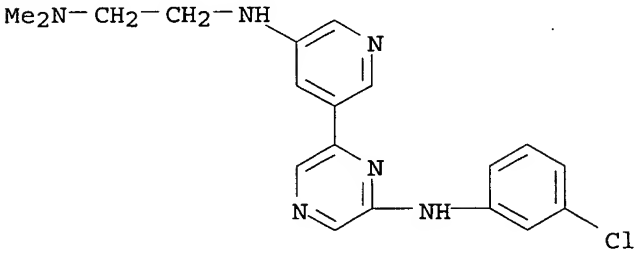
RN 405938-74-1 HCAPLUS
CN Ethanol, 2-[2-[2-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]ethoxy]ethoxy]- (9CI) (CA INDEX NAME)



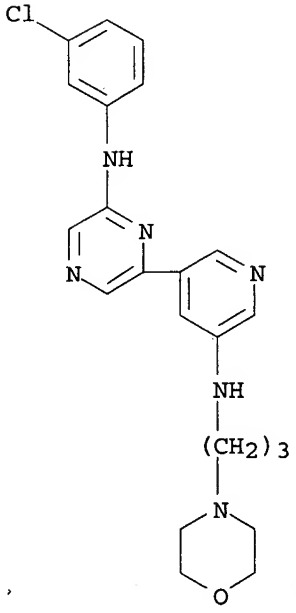
RN 405938-75-2 HCAPLUS
CN Pyrazinamine, 6-(5-amino-3-pyridinyl)-N-(3-chlorophenyl)- (9CI) (CA INDEX NAME)



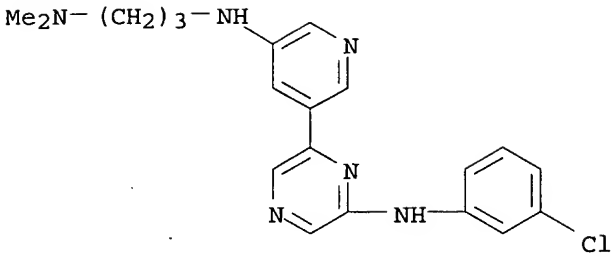
RN 405938-76-3 HCAPLUS
CN 1,2-Ethanediamine, N'-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-N,N-dimethyl- (9CI) (CA INDEX NAME)



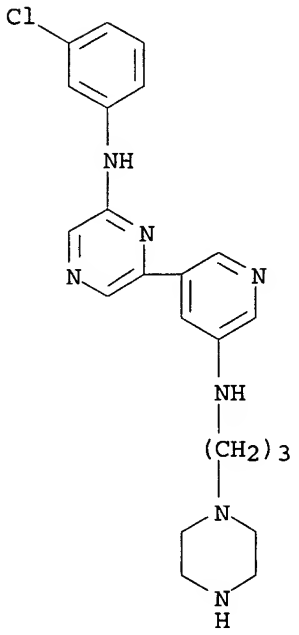
RN 405938-77-4 HCAPLUS
CN 4-Morpholinepropanamine, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]- (9CI) (CA INDEX NAME)



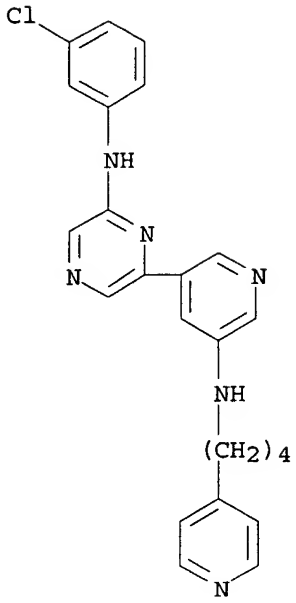
RN 405938-78-5 HCAPLUS
CN 1,3-Propanediamine, N'-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-N,N-dimethyl- (9CI) (CA INDEX NAME)



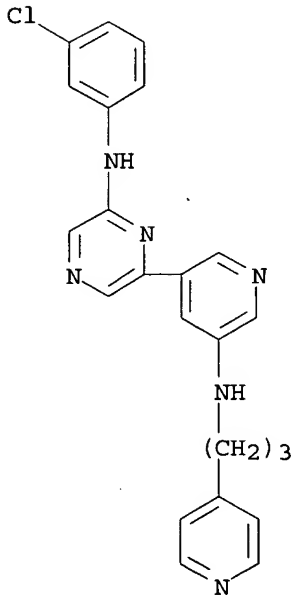
RN 405938-79-6 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(1-piperazinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



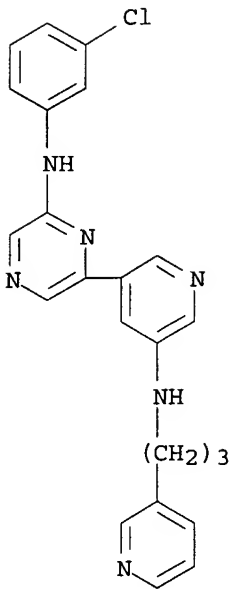
RN 405938-80-9 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[4-(4-pyridinyl)butyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



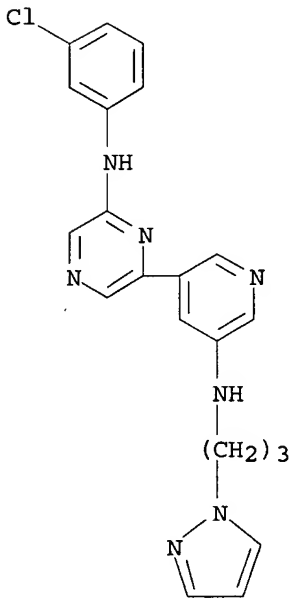
RN 405938-81-0 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(4-pyridinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



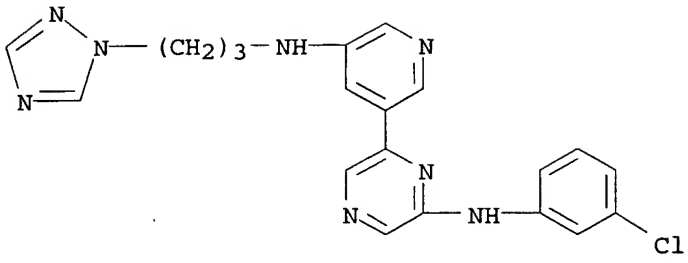
RN 405938-82-1 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(3-pyridinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



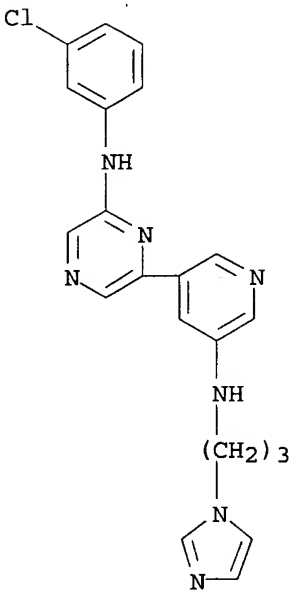
RN 405938-83-2 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(1H-pyrazol-1-yl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



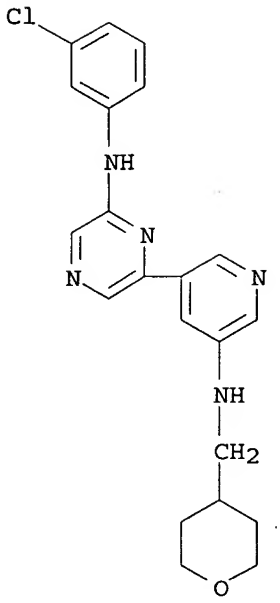
RN 405938-84-3 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(1H-1,2,4-triazol-1-yl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



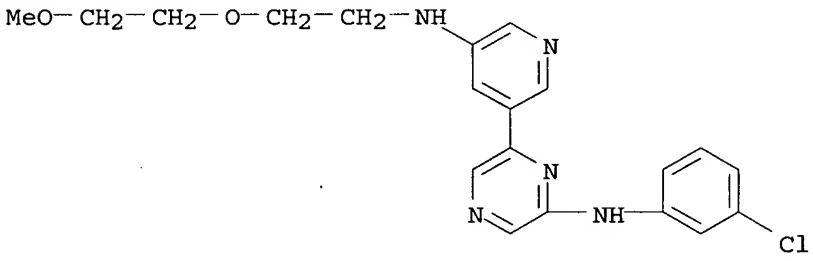
RN 405938-85-4 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(1H-imidazol-1-yl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



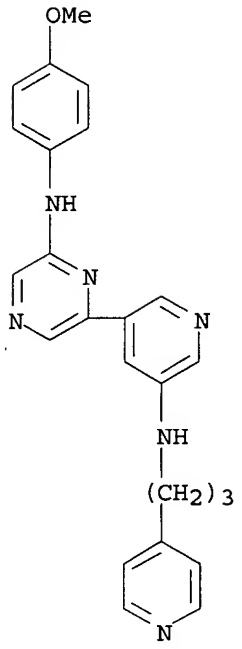
RN 405938-86-5 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[(tetrahydro-2H-pyran-4-yl)methyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



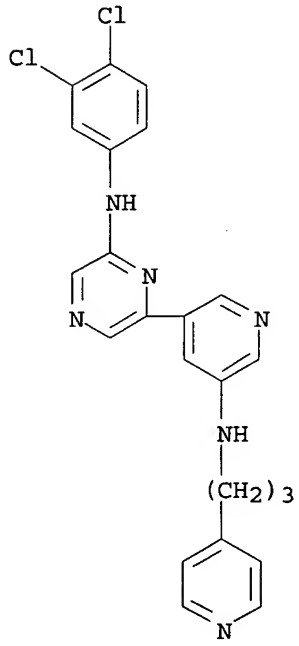
RN 405938-87-6 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[2-(2-methoxyethoxy)ethyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



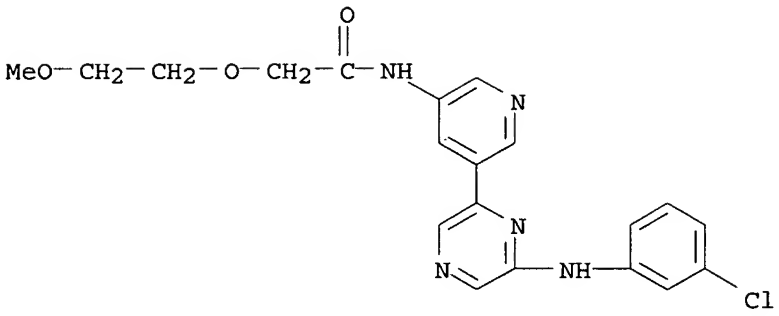
RN 405938-88-7 HCAPLUS
CN Pyrazinamine, N-(4-methoxyphenyl)-6-[5-[[3-(4-pyridinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



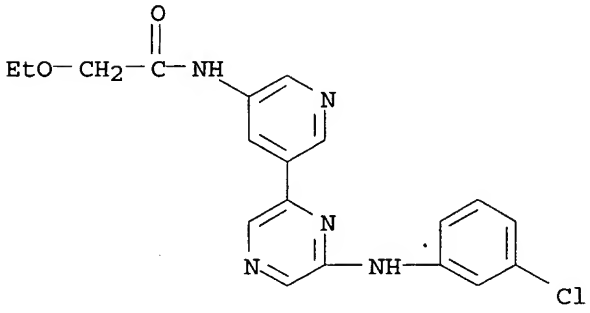
RN 405938-89-8 HCAPLUS
CN Pyrazinamine, N-(3,4-dichlorophenyl)-6-[5-[[3-(4-pyridinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



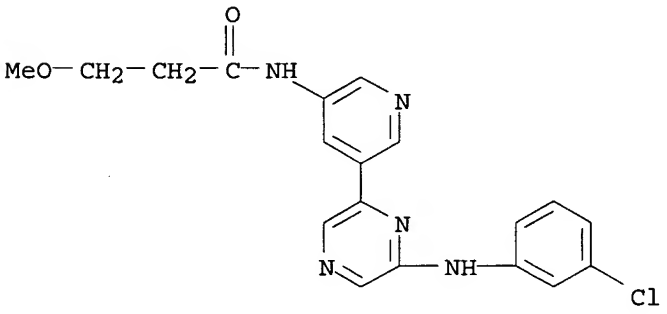
RN 405938-90-1 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-(2-methoxyethoxy)- (9CI) (CA INDEX NAME)



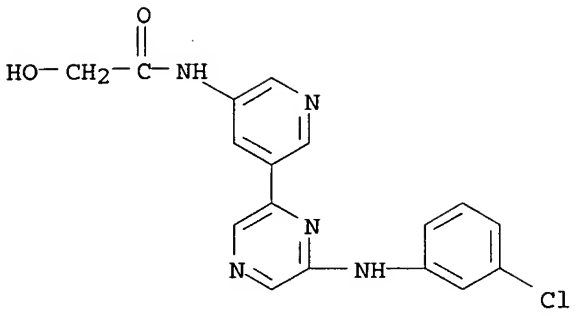
RN 405938-91-2 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-ethoxy- (9CI) (CA INDEX NAME)



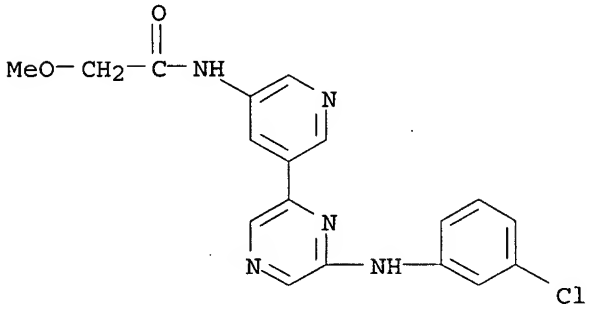
RN 405938-92-3 HCAPLUS
CN Propanamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-3-methoxy- (9CI) (CA INDEX NAME)



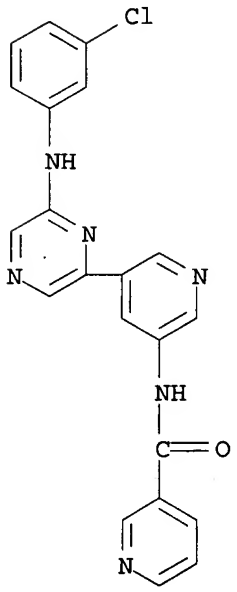
RN 405938-93-4 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-hydroxy- (9CI) (CA INDEX NAME)



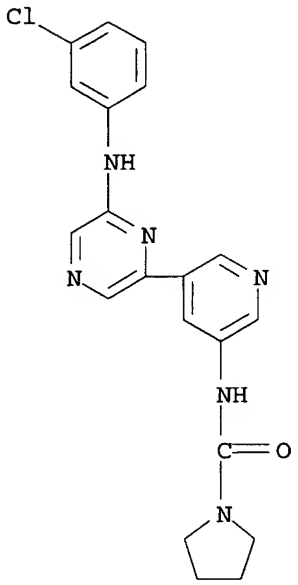
RN 405938-94-5 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-methoxy- (9CI) (CA INDEX NAME)



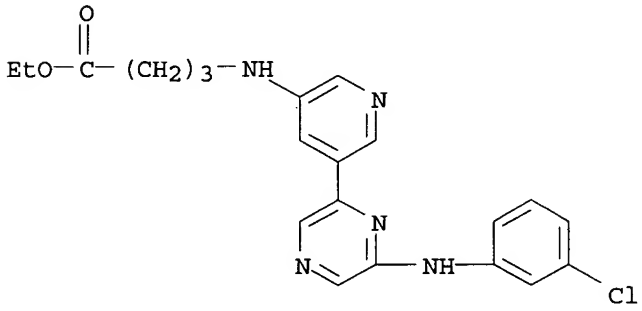
RN 405938-95-6 HCAPLUS
CN 3-Pyridinecarboxamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]- (9CI) (CA INDEX NAME)



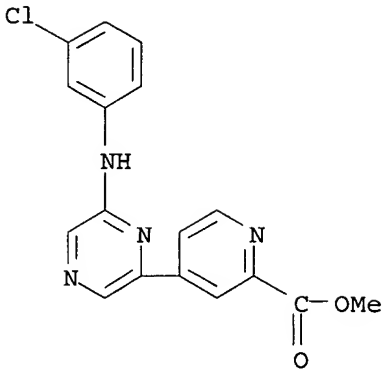
RN 405938-96-7 HCAPLUS
CN 1-Pyrrolidinecarboxamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]- (9CI) (CA INDEX NAME)



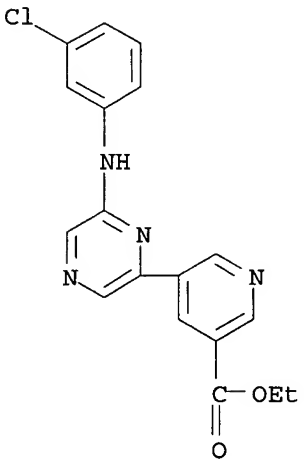
RN 405938-97-8 HCAPLUS
CN Butanoic acid, 4-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)



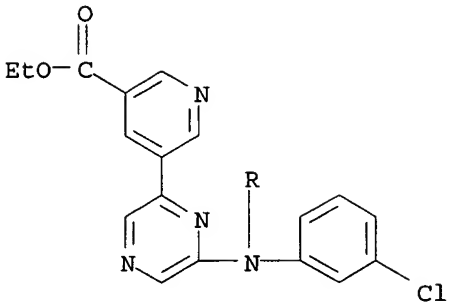
RN 405939-01-7 HCAPLUS
CN 2-Pyridinecarboxylic acid, 4-[6-[(3-chlorophenyl)amino]pyrazinyl]-, methyl ester (9CI) (CA INDEX NAME)

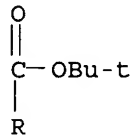


RN 405939-81-3 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

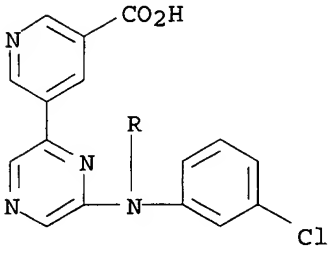


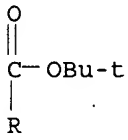
RN 405939-82-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



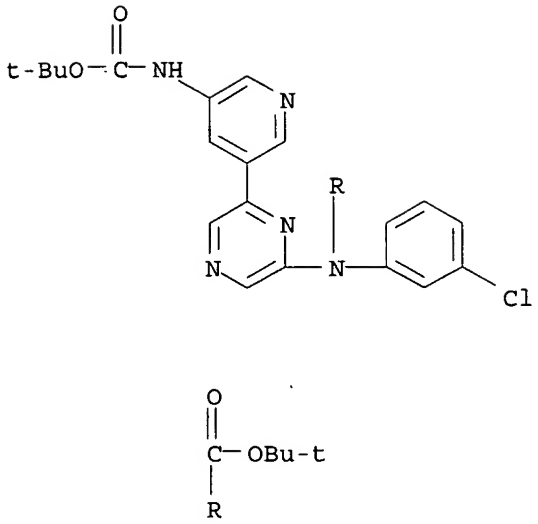


RN 405939-83-5 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]- (9CI) (CA INDEX NAME)

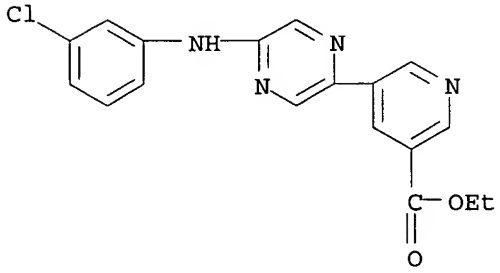




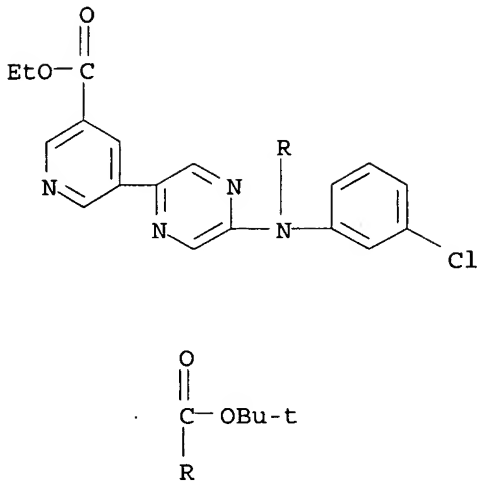
RN 405939-84-6 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



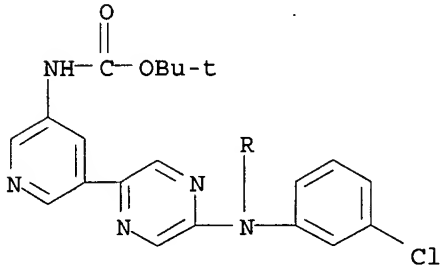
RN 405939-90-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[5-[(3-chlorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

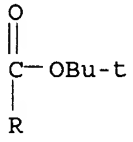


RN 405939-91-5 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[5-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

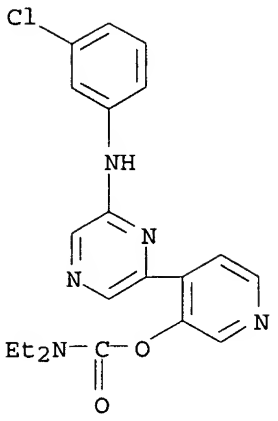


RN 405939-92-6 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[5-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

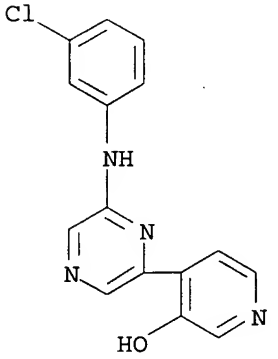




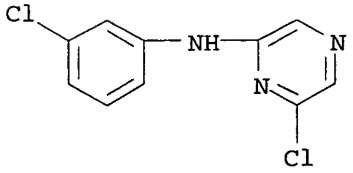
RN 405940-02-5 HCAPLUS
CN Carbamic acid, diethyl-, 4-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl ester (9CI) (CA INDEX NAME)



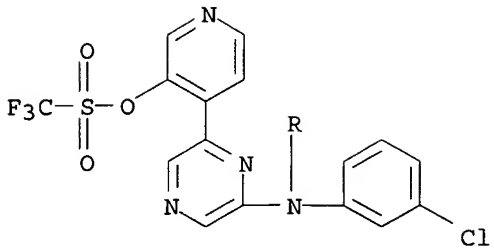
RN 405940-03-6 HCAPLUS
CN 3-Pyridinol, 4-[6-[(3-chlorophenyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)

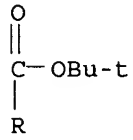


RN 405940-04-7 HCAPLUS
CN Pyrazinamine, 6-chloro-N-(3-chlorophenyl)- (9CI) (CA INDEX NAME)

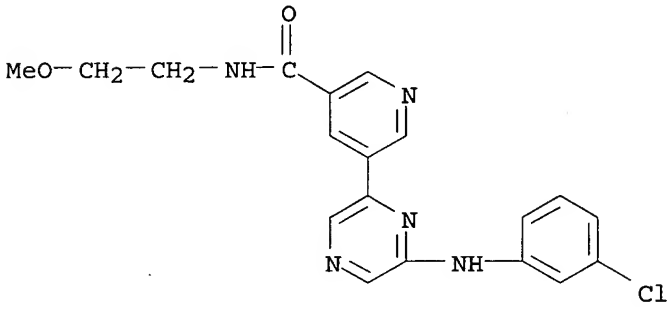


RN 405940-05-8 HCAPLUS
CN Methanesulfonic acid, trifluoro-, 4-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl ester (9CI) (CA INDEX NAME)

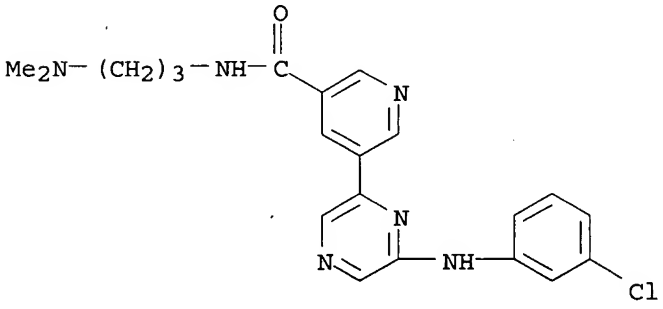




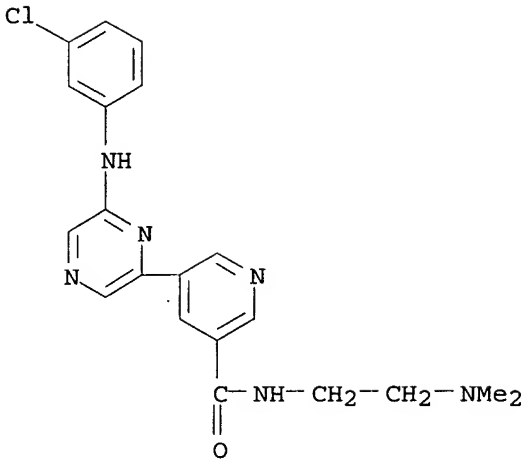
RN 405940-06-9 HCAPLUS
CN 3-Pyridinecarboxamide, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-N-(2-methoxyethyl)- (9CI) (CA INDEX NAME)



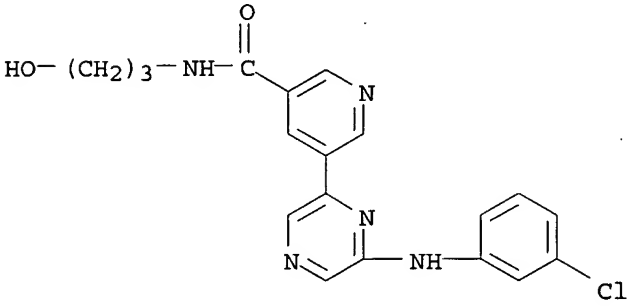
RN 405940-07-0 HCAPLUS
CN 3-Pyridinecarboxamide, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-N-[3-(dimethylamino)propyl]- (9CI) (CA INDEX NAME)



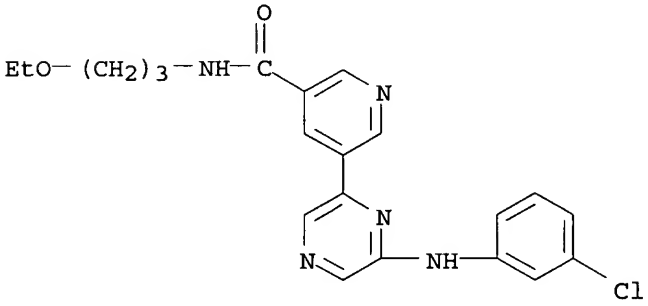
RN 405940-08-1 HCAPLUS
CN 3-Pyridinecarboxamide, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-N-[2-(dimethylamino)ethyl]- (9CI) (CA INDEX NAME)



RN 405940-09-2 HCAPLUS
CN 3-Pyridinecarboxamide, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-N-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



RN 405940-10-5 HCAPLUS
CN 3-Pyridinecarboxamide, 5-[6-[(3-chlorophenyl)amino]pyrazinyl]-N-(3-ethoxypropyl)- (9CI) (CA INDEX NAME)



RN 405940-11-6 HCAPLUS
CN Benzamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-4-(dimethylamino)- (9CI) (CA INDEX NAME)

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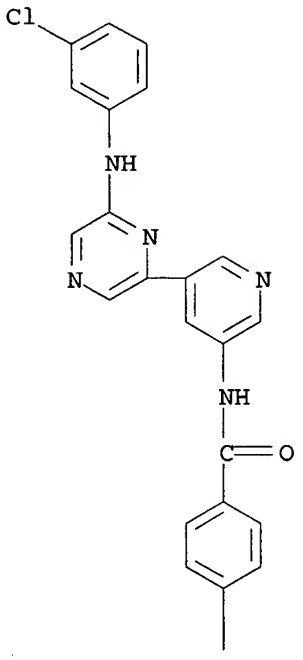

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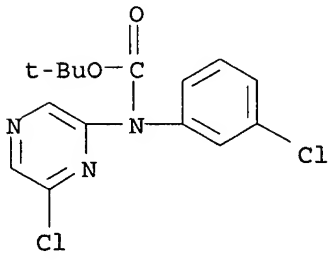
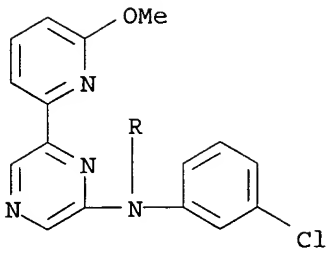
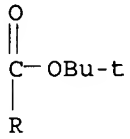
RN 405940-12-7 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)(6-chloropyrazinyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

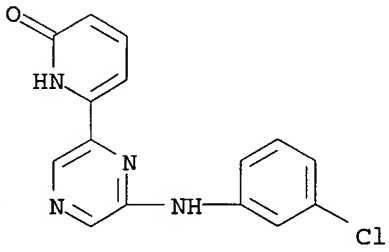


RN 405940-13-8 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6-(6-methoxy-2-pyridinyl)pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

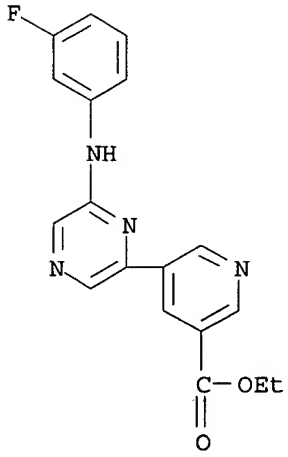




RN 405940-14-9 HCAPLUS
CN 2(1H)-Pyridinone, 6-[6-[(3-chlorophenyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)

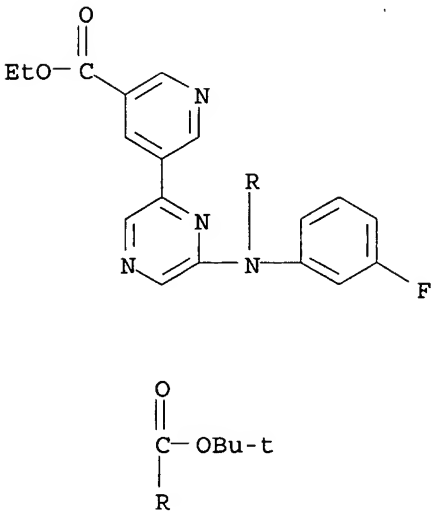


RN 405940-15-0 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-fluorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

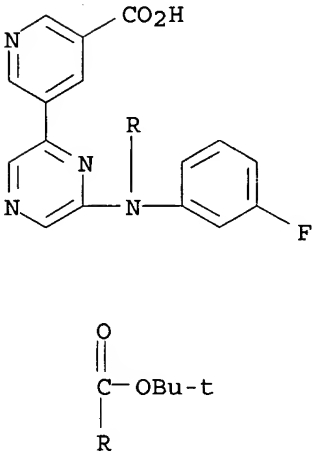


RN 405940-16-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](3-

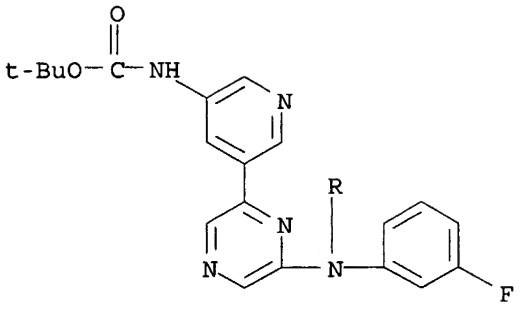
fluorophenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

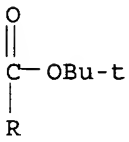


RN 405940-17-2 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](3-fluorophenyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)

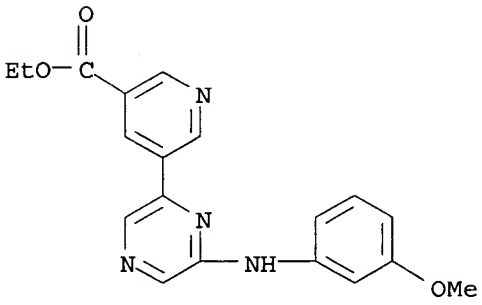


RN 405940-18-3 HCAPLUS
CN Carbamic acid, [6-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl](3-fluorophenyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

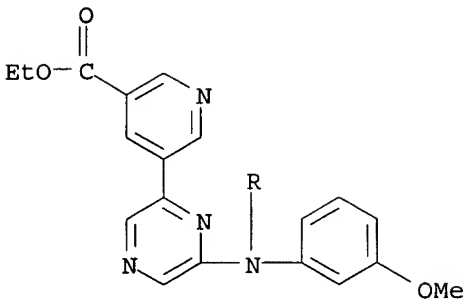


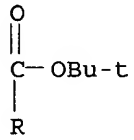


RN 405940-19-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(3-methoxyphenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)

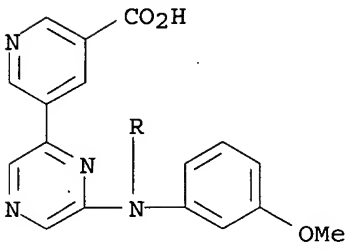


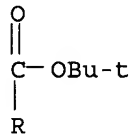
RN 405940-20-7 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](3-methoxyphenyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



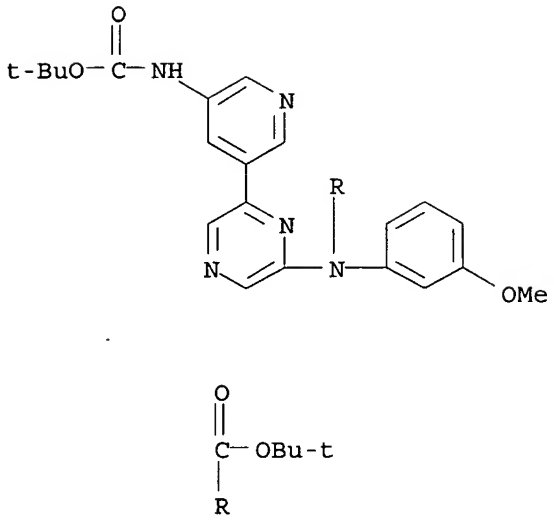


RN 405940-21-8 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](3-methoxyphenyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)

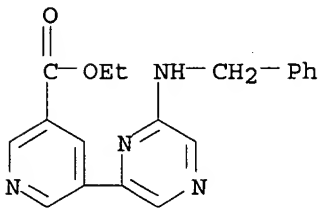




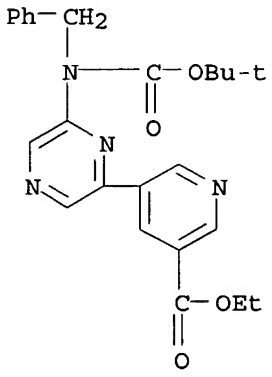
RN 405940-22-9 HCAPLUS
CN Carbamic acid, [6-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl](3-methoxyphenyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



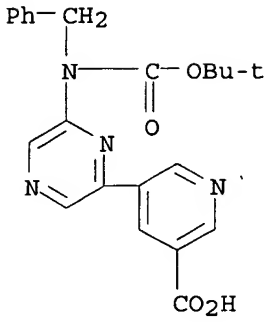
RN 405940-23-0 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[(phenylmethyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



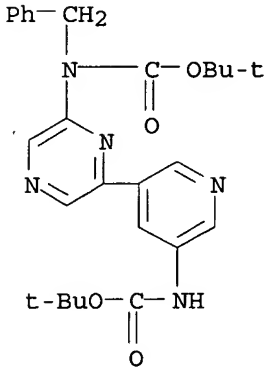
RN 405940-24-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](phenylmethyl)amino]pyrazinyl]-, ethyl ester (9CI) (CA INDEX NAME)



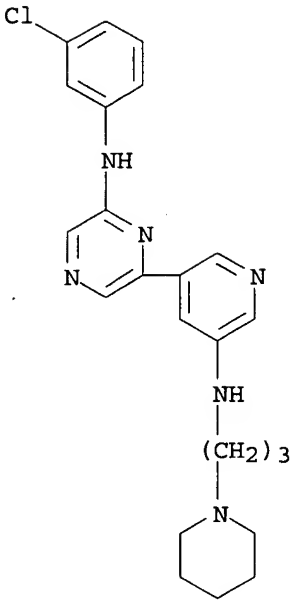
RN 405940-25-2 HCAPLUS
CN 3-Pyridinecarboxylic acid, 5-[6-[[(1,1-dimethylethoxy)carbonyl](phenylmethyl)amino]pyrazinyl]- (9CI) (CA INDEX NAME)



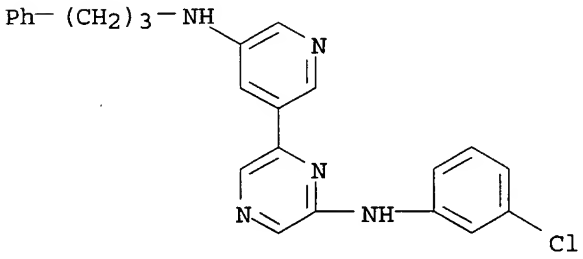
RN 405940-26-3 HCAPLUS
CN Carbamic acid, [6-[5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-pyridinyl]pyrazinyl](phenylmethyl)-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



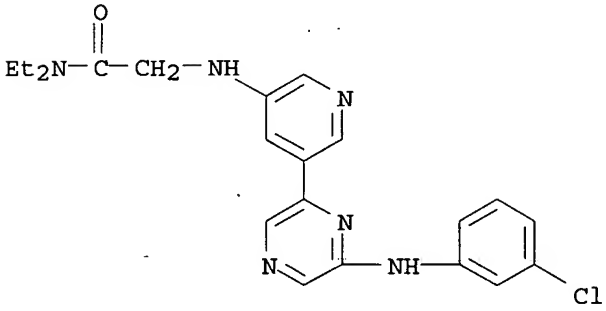
RN 405940-28-5 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-(1-piperidinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



RN 405940-29-6 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[(3-phenylpropyl)amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)

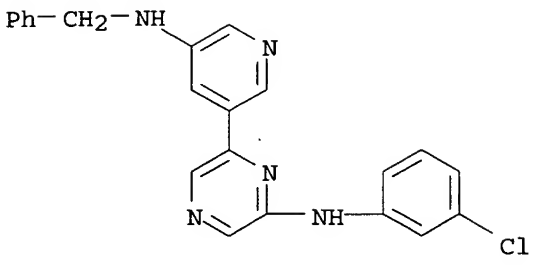


RN 405940-30-9 HCAPLUS
CN Acetamide, 2-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-N,N-diethyl- (9CI) (CA INDEX NAME)

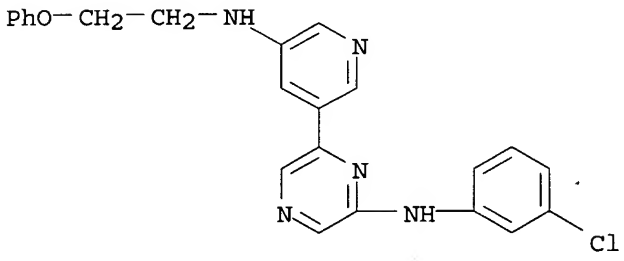


RN 405940-31-0 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[(phenylmethyl)amino]-3-pyridinyl]-

(9CI) (CA INDEX NAME)

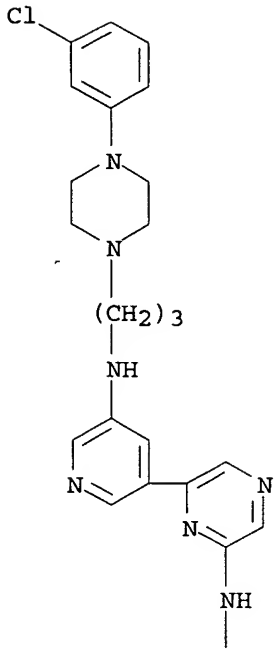


RN 405940-32-1 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[(2-phenoxyethyl)amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)

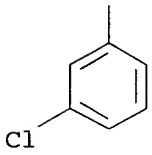


RN 405940-33-2 HCAPLUS
CN Pyrazinamine, N-(3-chlorophenyl)-6-[5-[[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)

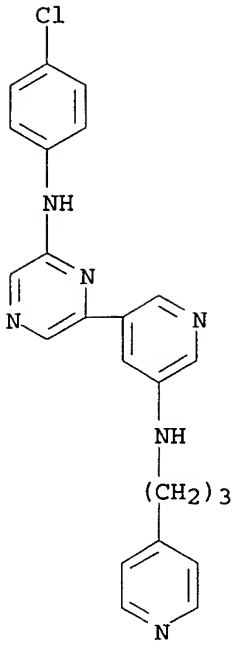
PAGE 1-A



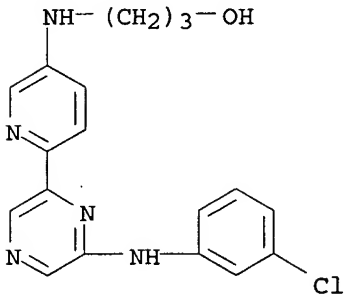
PAGE 2-A



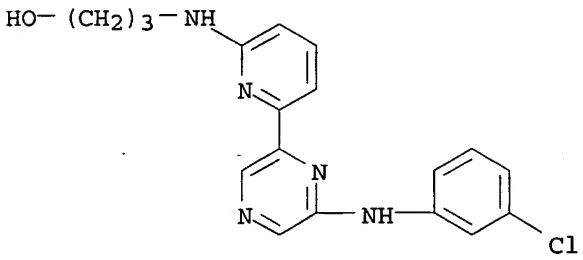
RN 405940-34-3 HCAPLUS
CN Pyrazinamine, N-(4-chlorophenyl)-6-[5-[[3-(4-pyridinyl)propyl]amino]-3-pyridinyl]- (9CI) (CA INDEX NAME)



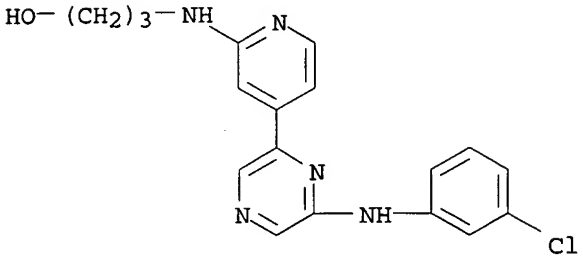
RN 405940-35-4 HCAPLUS
CN 1-Propanol, 3-[[6-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]-
(9CI) (CA INDEX NAME)



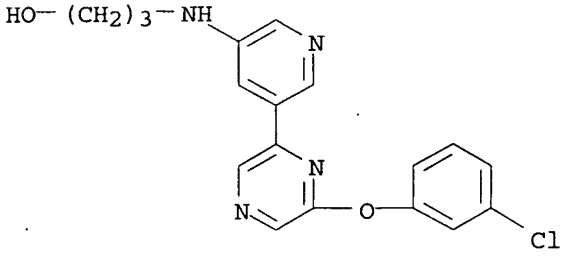
RN 405940-36-5 HCAPLUS
CN 1-Propanol, 3-[[6-[6-[(3-chlorophenyl)amino]pyrazinyl]-2-pyridinyl]amino]-
(9CI) (CA INDEX NAME)



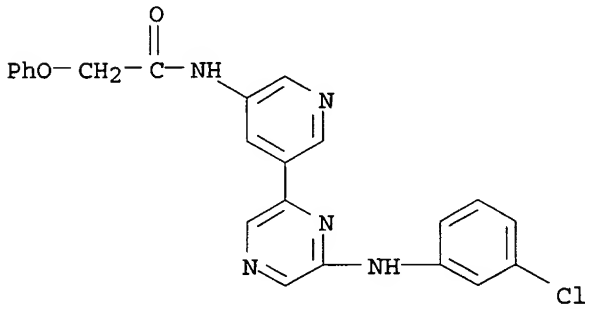
RN 405940-37-6 HCAPLUS
CN 1-Propanol, 3-[[4-[6-[(3-chlorophenyl)amino]pyrazinyl]-2-pyridinyl]amino]- (9CI) (CA INDEX NAME)



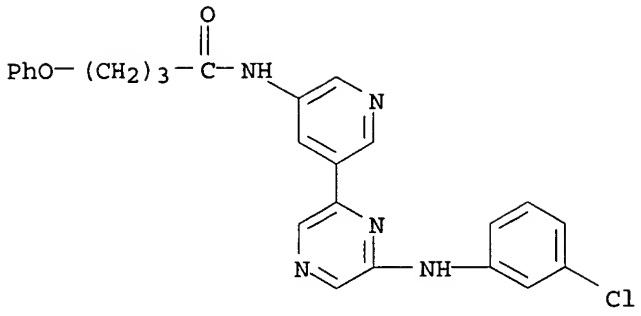
RN 405940-38-7 HCAPLUS
CN 1-Propanol, 3-[[5-[6-(3-chlorophenoxy)pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



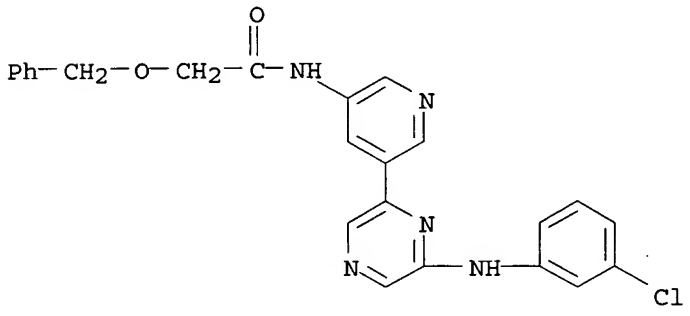
RN 405940-39-8 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-phenoxy- (9CI) (CA INDEX NAME)



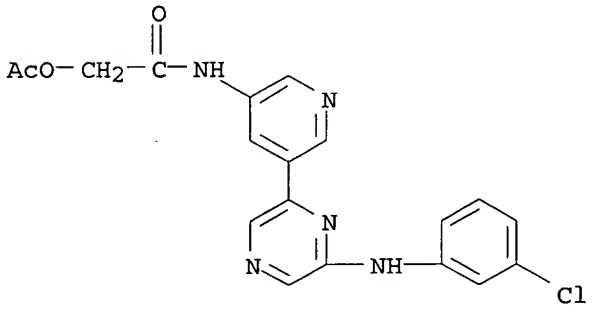
RN 405940-40-1 HCAPLUS
CN Butanamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-4-phenoxy- (9CI) (CA INDEX NAME)



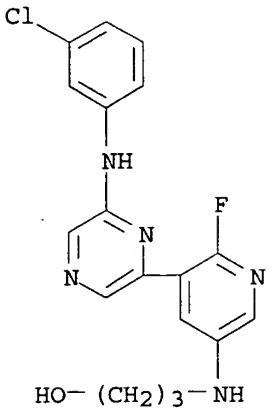
RN 405940-41-2 HCAPLUS
CN Acetamide, N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-2-(phenylmethoxy)- (9CI) (CA INDEX NAME)



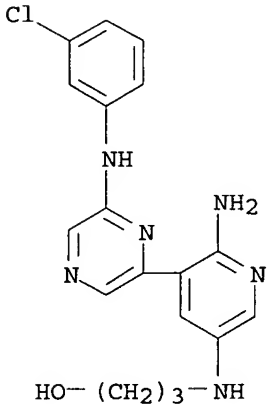
RN 405940-42-3 HCAPLUS
CN Acetamide, 2-(acetyloxy)-N-[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]- (9CI) (CA INDEX NAME)



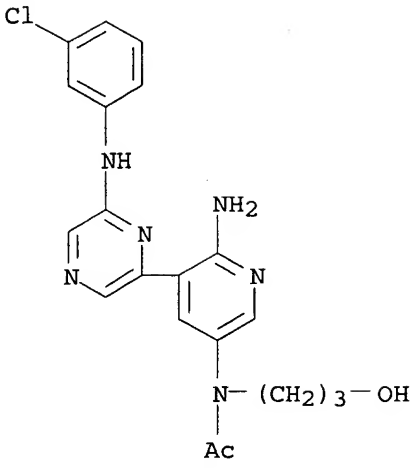
RN 405940-43-4 HCAPLUS
CN 1-Propanol, 3-[[5-[6-[(3-chlorophenyl)amino]pyrazinyl]-6-fluoro-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



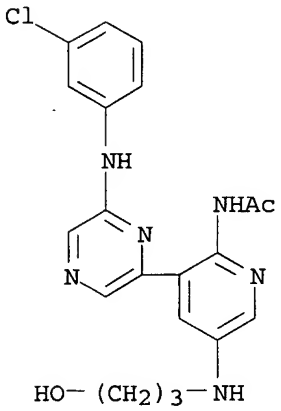
RN 405940-44-5 HCAPLUS
CN 1-Propanol, 3-[[6-amino-5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



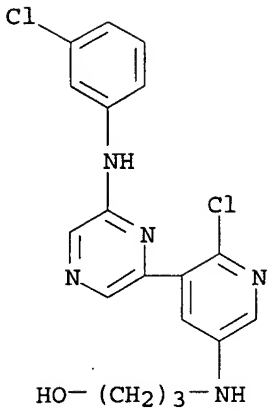
RN 405940-45-6 HCAPLUS
CN Acetamide, N-[6-amino-5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]-N-(3-hydroxypropyl)- (9CI) (CA INDEX NAME)



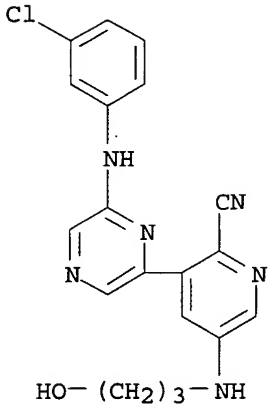
RN 405940-46-7 HCAPLUS
CN Acetamide, N-[3-[6-[(3-chlorophenyl)amino]pyrazinyl]-5-[(3-hydroxypropyl)amino]-2-pyridinyl]- (9CI) (CA INDEX NAME)



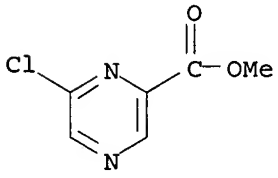
RN 405940-47-8 HCAPLUS
CN 1-Propanol, 3-[[6-chloro-5-[6-[(3-chlorophenyl)amino]pyrazinyl]-3-pyridinyl]amino]- (9CI) (CA INDEX NAME)



RN 405940-48-9 HCAPLUS
CN 2-Pyridinecarbonitrile, 3-[6-[(3-chlorophenyl)amino]pyrazinyl]-5-[(3-hydroxypropyl)amino]- (9CI) (CA INDEX NAME)



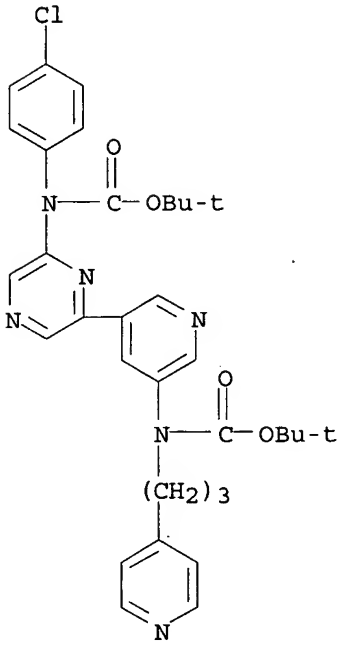
IT **23611-75-8**, Methyl 6-chloro-2-pyrazinecarboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrazines as **modulators** of vascular endothelial growth factor (VEGF) receptor tyrosine **kinase**)
RN 23611-75-8 HCAPLUS
CN Pyrazinecarboxylic acid, 6-chloro-, methyl ester (8CI, 9CI) (CA INDEX NAME)



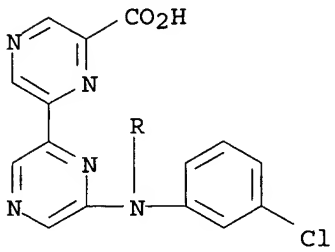
IT **405939-75-5P 405939-76-6P 405939-77-7P**
405939-78-8P 405939-80-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

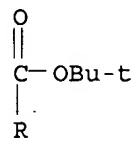
(Reactant or reagent)
(preparation of pyrazines as **modulators** of vascular endothelial growth factor (VEGF) receptor tyrosine **kinase**)

RN 405939-75-5 HCAPLUS
CN Carbamic acid, [5-[6-[(4-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]-3-pyridinyl][3-(4-pyridinyl)propyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



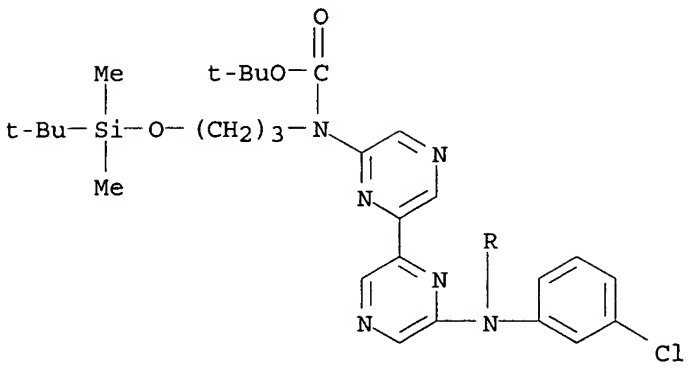
RN 405939-76-6 HCAPLUS
CN [2,2'-Bipyrazine]-6-carboxylic acid, 6'-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]- (9CI) (CA INDEX NAME)

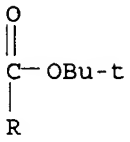




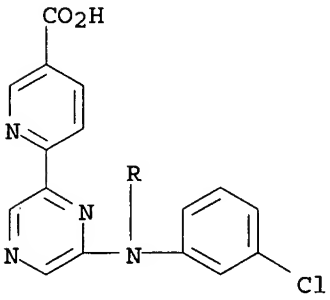
RN 405939-77-7 HCAPLUS
CN Carbamic acid, [6'-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino][2,2'-bipyrazin]-6-yl][3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-,

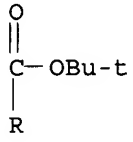
1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



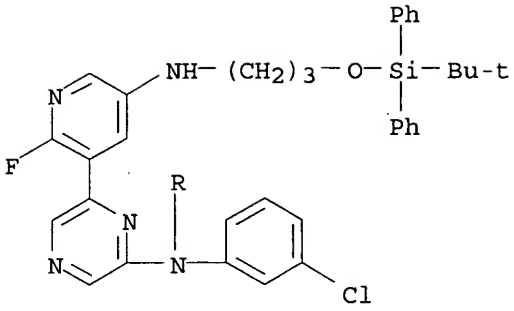


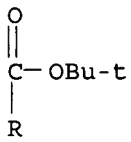
RN 405939-78-8 HCAPLUS
CN 3-Pyridinecarboxylic acid, 6-[6-[(3-chlorophenyl)[(1,1-dimethylethoxy)carbonyl]amino]pyrazinyl]- (9CI) (CA INDEX NAME)





RN 405939-80-2 HCAPLUS
CN Carbamic acid, (3-chlorophenyl)[6-[5-[[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]propyl]amino]-2-fluoro-3-pyridinyl]pyrazinyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)





L23 ANSWER 19 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:636071 HCAPLUS
DOCUMENT NUMBER: 135:195566
TITLE: Preparation of pyridinylimidazoles as ALK5 receptor modulators
INVENTOR(S): Gaster, Laramie Mary; Hadley, Michael Stewart; Harling, John David; Harrington, Frank Peter; Heer, Jag Paul; Heightman, Thomas Daniel
PATENT ASSIGNEE(S): Smithkline Beecham P.L.C., UK
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062756	A1	20010830	WO 2001-GB736	20010221 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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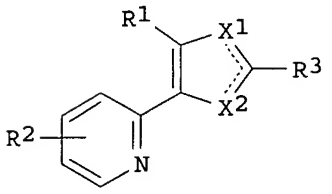
JP 2003524010	T2	20030812	JP 2001-562538	20010221
NZ 520753	A	20040827	NZ 2001-520753	20010221
NO 2002003953	A	20021021	NO 2002-3953	20020820
ZA 2002006642	A	20030714	ZA 2002-6642	20020820
US 2003166633	A1	20030904	US 2002-204370	20021029
US 2004220230	A1	20041104	US 2004-767943	20040129

PRIORITY APPLN. INFO.:

GB 2000-4053	A	20000221
GB 2000-15902	A	20000628
WO 2001-GB736	W	20010221
US 2002-204370	B1	20021029

OTHER SOURCE(S): MARPAT 135:195566

GI



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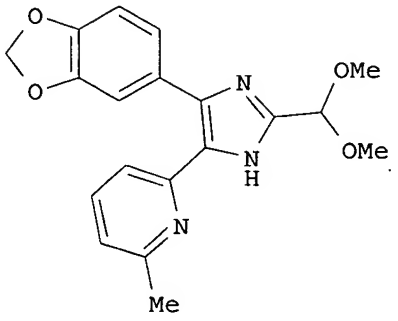


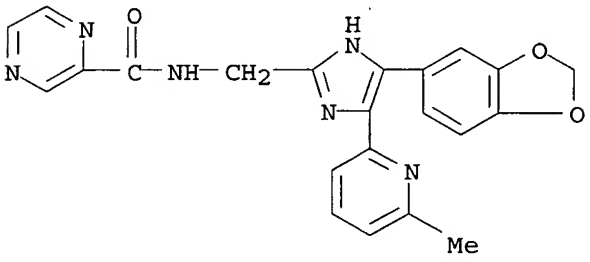
II

AB The title compds. [I; R1 = (un)substituted naphthyl, anthracenyl, Ph, etc.; R2 = H, alkyl, alkoxy, etc.; R3 = alkyl, (CH2)pCN, (CH2)pCO2H, etc.; one of X1 and X2 = N and the other = NR10; R10 = H, alkyl, cycloalkyl] and their pharmaceutically acceptable salts, useful in inhibiting the TGF-β signaling pathway in mammals, were prepared Thus, treating 1-(benzo[1,3]dioxol-5-yl)-2-(6-methylpyridin-2-yl)ethane-1,2-dione (preparation given) with glyoxal 1,1-dimethylacetal in tert-Bu Me ether followed by addition of ammonium acetate afforded 91% II. The compds. I generally show ALK5 receptor modulator activity having IC50 values in the range of 0.0001 to 10 μM.

IT **356559-66-5P 356560-18-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyridinylimidazoles as ALK5 receptor modulators)

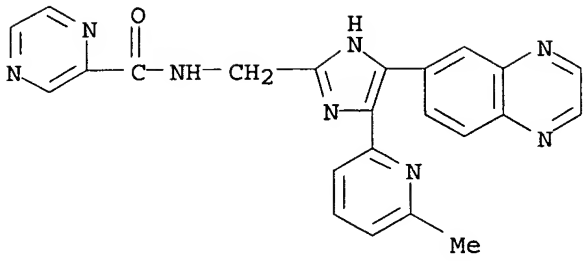
RN 356559-66-5 HCAPLUS

CN Pyrazinecarboxamide, N-[[4-(1,3-benzodioxol-5-yl)-5-(6-methyl-2-pyridinyl)-1H-imidazol-2-yl]methyl]- (9CI) (CA INDEX NAME)



RN 356560-18-4 HCAPLUS

CN Pyrazinecarboxamide, N-[[4-(6-methyl-2-pyridinyl)-5-(6-quinoxalinyl)-1H-imidazol-2-yl]methyl]- (9CI) (CA INDEX NAME)



IT **199015-85-5**, activin receptor like-**kinase**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of pyridinylimidazoles as ALK5 receptor **modulators**)
RN 199015-85-5 HCAPLUS
CN Kinase (phosphorylating), activin receptor-like (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 20 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:545464 HCAPLUS
DOCUMENT NUMBER: 135:127207
TITLE: Combinations comprising dipeptidylpeptidase-IV inhibitor
INVENTOR(S): Balkan, Boerk; Hughes, Thomas Edward; Holmes, David Grenville; Villhauer, Edwin Bernard
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052825	A2	20010726	WO 2001-EP590	20010119 <--
WO 2001052825	A3	20020328		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2397554	AA	20010726	CA 2001-2397554	20010119 <--
EP 1248604	A2	20021016	EP 2001-909661	20010119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001007715	A	20021119	BR 2001-7715	20010119
JP 2003520226	T2	20030702	JP 2001-552873	20010119
US 2003139434	A1	20030724	US 2002-181169	20021010
PRIORITY APPLN. INFO.:			US 2000-489234 A	20000121

US 2000-619262 A 20000719
WO 2001-EP590 W 20010119

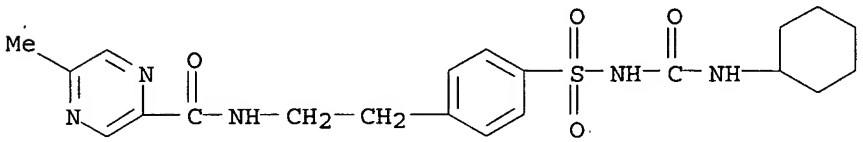
OTHER SOURCE(S): MARPAT 135:127207

AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compound, preferably selected from the group consisting of insulin signalling pathway **modulators**, like inhibitors of protein tyrosine phosphatases (PTPases), non-small mol. mimetic compds. and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compds. influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase **kinase** (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, α-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and α2-adrenergic antagonists, for simultaneous, sep. or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase - IV (DPP-IV), in particular diabetes, more especially type 2 diabetes mellitus, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body weight Tablets were prepared containing nateglinide.

IT **29094-61-9**, Glipizide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations comprising dipeptidylpeptidase-IV inhibitor)

RN 29094-61-9 HCAPLUS

CN Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl- (9CI) (CA INDEX NAME)



L23 ANSWER 21 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:412094 HCAPLUS
DOCUMENT NUMBER: 135:174873
TITLE: 26S proteasome inhibition induces apoptosis and limits growth of human pancreatic cancer
AUTHOR(S): Shah, Shimul A.; Potter, Michael W.; McDade, Theodore P.; Ricciardi, Rocco; Perugini, Richard A.; Elliott, Peter J.; Adams, Julian; Callery, Mark P.
CORPORATE SOURCE: Department of Surgery, University of Massachusetts Medical School, Worcester, MA, 01655, USA
SOURCE: Journal of Cellular Biochemistry (**2001**), 82(1), 110-122
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 26S proteasome degrades proteins that **regulate** transcription factor activation, cell cycle progression, and apoptosis. In cancer, this may allow for uncontrolled cell division, promoting tumor growth, and spread. We examined whether selective inhibition of the 26S proteasome with

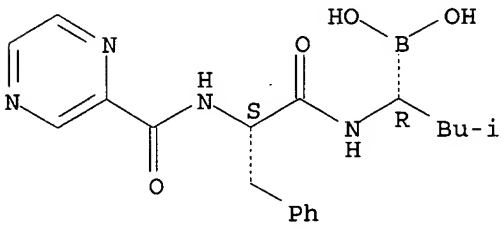
PS-341, a dipeptide boronic acid analog, would block proliferation and induce apoptosis in human pancreatic cancer. Proteasome inhibition significantly blocked mitogen (FCS) induced proliferation of BxPC3 human pancreatic cancer cells in vitro, while arresting cell cycle progression and inducing apoptosis by 24 h. Accumulation of p21Cip1-Waf-1, a cyclin dependent **kinase** (CDK) inhibitor normally degraded by the 26S proteasome, occurred by 3 h and correlated with cell cycle arrest. When BxPC3 pancreatic cancer xenografts were established in athymic nu/nu mice, weekly administration of 1 mg/kg PS-341 significantly inhibited tumor growth. Both cellular apoptosis and p21Cip1-Waf-1 protein levels were increased in PS-341 treated xenografts. Inhibition of tumor xenograft growth was greatest (89%) when PS-341 was combined with the tumoricidal agent CPT-11. Combined CPT-11/PS-341 therapy, but not single agent therapy, yielded highly apoptotic tumors, significantly inhibited tumor cell proliferation, and blocked NF-κB activation indicating this systemic therapy was effective at the cancer cell level. 26S proteasome inhibition may represent a new therapeutic approach against this highly resistant and lethal malignancy.

IT **179324-69-7**, PS-341
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(26S proteasome inhibition induces apoptosis and limits growth of human pancreatic cancer)

RN 179324-69-7 HCAPLUS

CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 22 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:394968 HCAPLUS

DOCUMENT NUMBER: 135:205090

TITLE: Proteasome- and p38-dependent regulation of ERK3 expression

AUTHOR(S): Zimmermann, Johann; Lamerant, Nathalie; Grossenbacher, Rita; Furst, Peter

CORPORATE SOURCE: Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.

SOURCE: Journal of Biological Chemistry (**2001**), 276(14), 10759-10766
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

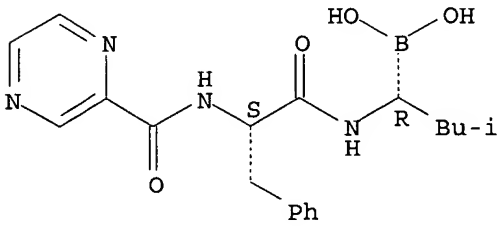
AB Proteasome inhibition leads to accumulation of transcription factors, heat

shock proteins, cyclins, and other proteasome substrate proteins by blocking their proteolytic degradation An increase in gene transcription upon proteasome inhibition was found for a group of proteins, including p21WAF1/CIP1, ubiquitin, and transcription factors. In this study, we have demonstrated selective up-**regulation** of extracellular signal-**regulated kinase** 3 (ERK3) mRNA and protein expression upon treatment with peptide-based proteasome inhibitors or lactacystin. ERK3 is a family member of the mitogen-activated protein **kinases** (also called ERK) that are key mediators of signal transduction from the cell surface to the nucleus. ERK3 up-**regulation** is independent of the p53, Bcl2, and caspase 3 status of cells. P38 pathway **kinase** inhibitors prevent proteasome-dependent ERK3 induction and enhance the antiproliferative effect of proteasome inhibitors. MCF-7 cells expressing ERK3 ectopically show increased resistance toward proteasome inhibition. The results indicate that ERK3 expression is a consequence of p38 pathway activation and most probably represents an intracellular defense or rescue mechanism against cell stress and damage induced by proteasome inhibition.

IT **144713-50-8**, protein **kinase** ERK3
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(proteasome- and p38-dependent **regulation** of ERK3 expression induced by proteasome inhibitors)
RN 144713-50-8 HCAPLUS
CN Kinase (phosphorylating), protein, ERK3 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **179324-69-7**, PS341
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteasome- and p38-dependent regulation of ERK3 expression induced by proteasome inhibitors)
RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 23 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:338762 HCAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103 <--
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

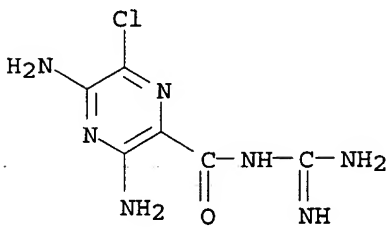
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

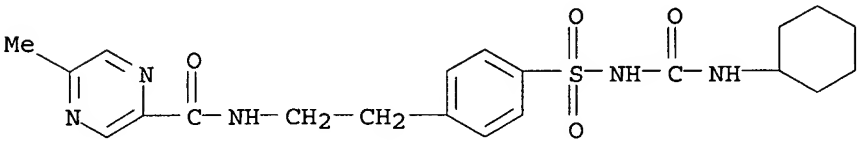
IT **2609-46-3**, Amiloride **29094-61-9**, Glipizide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)

RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



RN 29094-61-9 HCAPLUS

CN Pyrazinecarboxamide, N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methyl- (9CI) (CA INDEX NAME)



IT **137632-07-6**, Extracellular-signal-**regulated** **kinase** 1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)
RN 137632-07-6 HCAPLUS
CN Kinase (phosphorylating), protein, ERK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

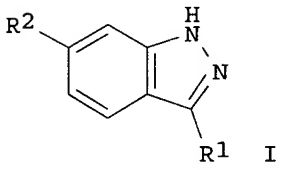
L23 ANSWER 24 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:31473 HCAPLUS
DOCUMENT NUMBER: 134:100864
TITLE: Indazole compounds and pharmaceutical compositions for inhibiting protein kinases, and methods for their use
INVENTOR(S): Kania, Robert Steven; Bender, Steven Lee; Borchardt, Allen J.; Braganza, John F.; Cripps, Stephan James; Hua, Ye; Johnson, Michael David; Johnson, Theodore Otto, Jr.; Luu, Hiep The; Palmer, Cynthia Louise; Reich, Siegfried Heinz; Tempczyk-russell, Anna Maria; Teng, Min; Thomas, Christine; Varney, Michael David; Wallace, Michael Brennan
PATENT ASSIGNEE(S): Agouron Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 439 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001002369	A2	20010111	WO 2000-US18263	20000630 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2383630	AA	20010111	CA 2000-2383630	20000630 <--
BR 2000012352	A	20020514	BR 2000-12352	20000630 <--
EP 1218348	A2	20020703	EP 2000-943375	20000630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

JP 2003503481	T2	20030128	JP 2001-507809		20000630
NZ 516676	A	20030926	NZ 2000-516676		20000630
AU 777701	B2	20041028	AU 2000-57852		20000630
NO 2001005797	A	20020301	NO 2001-5797		20011128 <--
ZA 2001010061	A	20030206	ZA 2001-10061		20011206
BG 106380	A	20020930	BG 2002-106380		20020201
HK 1048813	A1	20041210	HK 2003-101000		20030212
US 2004171634	A1	20040902	US 2003-326755		20030213
PRIORITY APPLN. INFO.:			US 1999-142130P	P	19990702
			US 2000-609335	B3	20000630
			WO 2000-US18263	W	20000630
			US 2001-983786	A3	20011025

OTHER SOURCE(S): MARPAT 134:100864

GI



I

AB Indazole compds. I [R1 = substituted or unsubstituted aryl or heteroaryl, R3CH:CH, R3N:CH; R2 = substituted or unsubstituted aryl, heteroaryl, Y-X; R3 = substituted or unsubstituted alkyl alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl; Y = O, S, C(:CH2), CO, SO, SO2, alkylidene, NH, N(C1-C8 alkyl); X = substituted or unsubstituted aryl, heteroaryl, NH(alkyl), NH(cycloalkyl), NH(heterocycloalkyl), NH(aryl), NH(heteroaryl), NH(alkoxy), NH(dialkylamide)] and their pharmaceutically acceptable prodrugs, active metabolites, and salts are disclosed. The compds. **modulate** and/or inhibit the activity of certain protein **kinases.** In particular, I and pharmaceutical compns. containing them are capable of mediating tyrosine **kinase** signal transduction, and thereby **modulate** and/or inhibit unwanted cell proliferation. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical compns. containing such compds., and to methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation, such as diabetic retinopathy, neovascular glaucoma, rheumatoid arthritis, and psoriasis, by administering effective amts. of such compds. E.g., I [R1 = (E)-3,4-(MeO)2C6H3CH:CH; R2 = 4-HO-3-MeOC6H3] (II) was prepared from 6-aminoindazole by diazotization and substitution with iodide, protection of the indazole nitrogen with 2,4,6-Me3C6H2SO2Cl, coupling of the regioisomeric mixture with 4-(methoxymethoxy)-3-methoxybenzeneboronic acid in the presence of dichlorobis(triphenylphosphine)palladium, and deprotection of the indazole moiety and iodination at the 3-position of the indazole. Treatment of the 3-indazolyl iodide with sec-butyllithium, phenyllithium, and DMF, regioselective protection of the indazole with 2,4,6-Me3C6H2SO2Cl, olefination with 3,4-dimethoxybenzyltriphenylphosphonium bromide, deprotection of the indazole, deprotection of the methoxymethyl group, and equilibration of the double bond with iodine gave II. Biol. data on protein **kinase** inhibition, cell proliferation inhibition, neovascularization inhibition, and i.p. and oral bioavailability, are given.

IT **9001-88-1**, Phosphorylase **kinase 9026-43-1**,

Protein **kinase 80449-02-1**, Tyrosine **kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of aryl-substituted indazole derivs. as **modulators** and inhibitors of protein **kinases** in the treatment of tumor growth, cellular proliferation, and angiogenesis)
RN 9001-88-1 HCAPLUS
CN Kinase (phosphorylating), phosphorylase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9026-43-1 HCAPLUS
CN Kinase (phosphorylating), protein serine/threonine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 80449-02-1 HCAPLUS
CN Kinase (phosphorylating), protein (tyrosine) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **114051-78-4**, Lck tyrosine **kinase 125149-26-0**, FGF receptor **kinase 141349-86-2**, Cdk2 **kinase 141350-03-0**, Flt-1 VEGF receptor tyrosine **kinase**
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of aryl-substituted indazole derivs. as **modulators** and inhibitors of protein **kinases** in the treatment of tumor growth, cellular proliferation, and angiogenesis)
RN 114051-78-4 HCAPLUS
CN Kinase (phosphorylating), protein p56lck (9CI) (CA INDEX NAME)

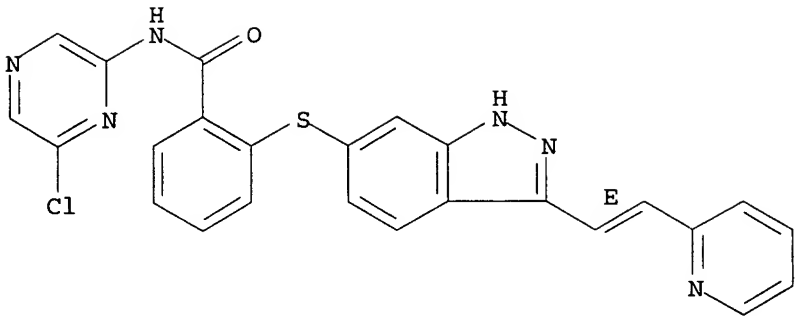
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 125149-26-0 HCAPLUS
CN Kinase (phosphorylating), fibroblast growth factor receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141349-86-2 HCAPLUS
CN Kinase (phosphorylating), gene cdk2 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141350-03-0 HCAPLUS
CN Kinase (phosphorylating), vascular endothelial growth factor receptor, gene flt-1 (9CI) (CA INDEX NAME)

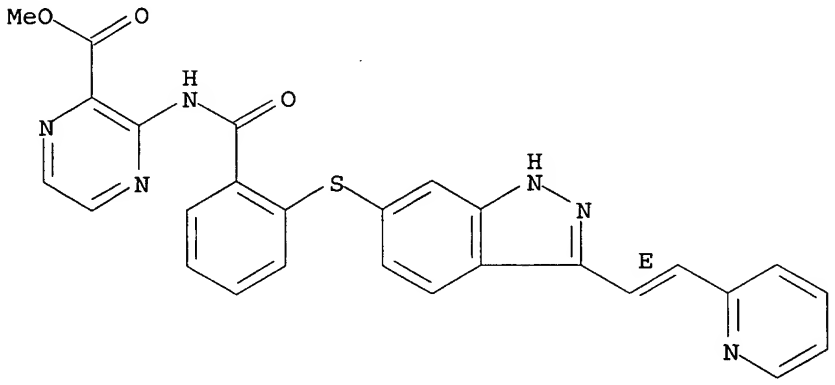
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **319468-87-6P 319469-28-8P 319470-87-6P 319472-34-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of combinatorial libraries of aryl-substituted indazole derivs. as **modulators** and inhibitors of protein **kinases** in the treatment of tumor growth, cellular proliferation, and angiogenesis)
RN 319468-87-6 HCAPLUS
CN Benzamide, N-(6-chloropyrazinyl)-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



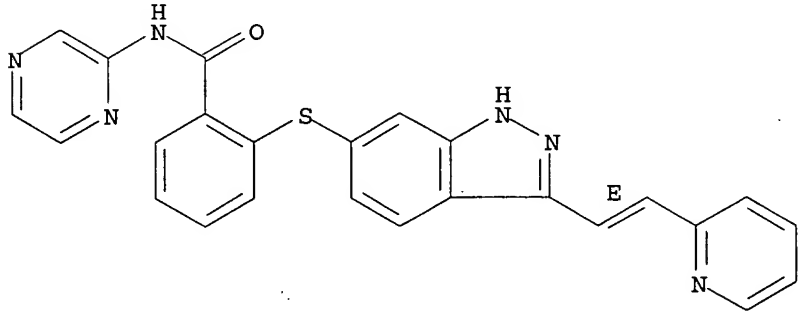
RN 319469-28-8 HCAPLUS
CN Pyrazinecarboxylic acid, 3-[[2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]benzoyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

Double bond geometry as shown.

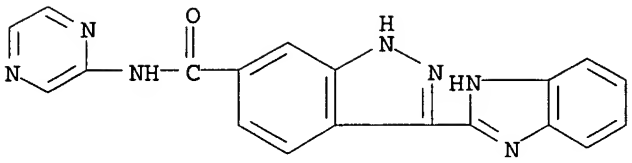


RN 319470-87-6 HCAPLUS
CN Benzamide, N-pyrazinyl-2-[[3-[(1E)-2-(2-pyridinyl)ethenyl]-1H-indazol-6-yl]thio]- (9CI) (CA INDEX NAME)

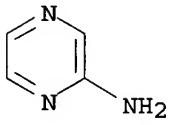
Double bond geometry as shown.



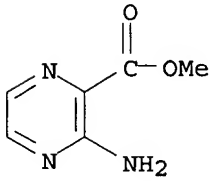
RN 319472-34-9 HCAPLUS
CN 1H-Indazole-6-carboxamide, 3-(1H-benzimidazol-2-yl)-N-pyrazinyl- (9CI) (CA INDEX NAME)



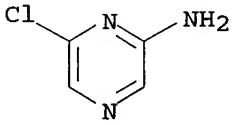
IT **5049-61-6**, Pyrazinamine **16298-03-6 33332-28-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of combinatorial libraries of aryl-substituted indazole derivs. as **modulators** and inhibitors of protein **kinases** in the treatment of tumor growth, cellular proliferation, and angiogenesis)
RN 5049-61-6 HCAPLUS
CN Pyrazinamine (9CI) (CA INDEX NAME)



RN 16298-03-6 HCAPLUS
CN Pyrazinecarboxylic acid, 3-amino-, methyl ester (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 33332-28-4 HCAPLUS
CN Pyrazinamine, 6-chloro- (9CI) (CA INDEX NAME)



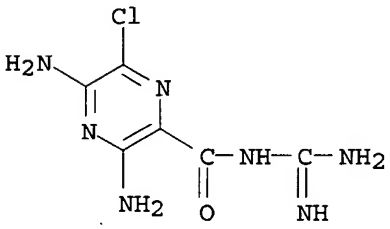
L23 ANSWER 25 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:910899 HCAPLUS
DOCUMENT NUMBER: 134:191794
TITLE: Inhibition of amiloride-sensitive epithelial Na+ absorption by extracellular nucleotides in human normal and cystic fibrosis airways
AUTHOR(S): Mall, Marcus; Wissner, Andreas; Gonska, Tanja; Calenborn, Detlef; Kuehr, Joachim; Brandis, Matthias; Kunzelmann, Karl

CORPORATE SOURCE: Universitats-Kinderklinik, Albert-Ludwigs Universitat Freiburg, Freiburg, 79106, Germany
SOURCE: American Journal of Respiratory Cell and Molecular Biology (**2000**), 23(6), 755-761
CODEN: AJRBEL; ISSN: 1044-1549
PUBLISHER: American Thoracic Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cystic fibrosis (CF) airway epithelia are characterized by enhanced Na+ absorption probably due to a lack of downregulation of epithelial Na+ channels by mutant CF transmembrane conductance **regulator.** Extracellular nucleotides ATP and UTP have been shown to activate alternative Ca2+-dependent Cl- channels in normal and CF respiratory epithelia. Recent studies suggest addnl. **modulation** of Na+ absorption by extracellular nucleotides. In this study, the role of mucosal ATP and UTP in **regulating** Na+ transport in native human upper airway tissues from patients with 16 patients with CF and 32 non-CF control subjects was examined To that end, transepithelial voltage and equivalent short-circuit current (Isc) were assessed by a perfused micro-Ussing chamber. Mucosal ATP and UTP caused an initial increase in lumen-neg. Isc that was followed by a sustained decrease of Isc in both non-CF and CF tissues. The amiloride-sensitive portion of Isc was inhibited in normal and CF tissues in the presence of either ATP or UTP. Both basal Na+ transport and nucleotide-dependent inhibition of amiloride-sensitive Isc were enhanced in CF airways compared with non-CF. Nucleotide-mediated inhibition of Na+ absorption was attenuated by pretreatment with the Ca2+-ATPase inhibitor cyclopiazonic acid but not by inhibition of protein **kinase** C with bisindolylmaleimide. These data demonstrate sustained inhibition of Na+ transport in non-CF and CF airways by mucosal ATP and UTP and suggest that this effect is mediated by an increase of intracellular Ca2+. Because ATP and UTP inhibit Na+ absorption and stimulate Cl- secretion simultaneously, extracellular nucleotides could have a dual therapeutic effect, counteracting the ion transport defect in CF lung disease.

IT **2609-46-3**, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(inhibition of amiloride-sensitive epithelial Na+ absorption by extracellular nucleotides in human normal and cystic fibrosis airways)

RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 26 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:368538 HCAPLUS

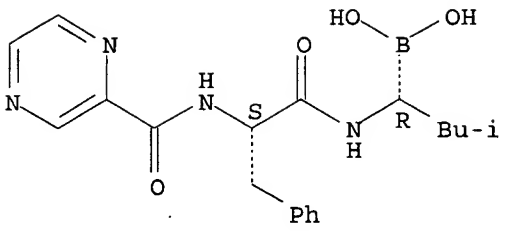
DOCUMENT NUMBER: 131:153427
TITLE: Proteasome inhibitors: a novel class of potent and effective antitumor agents
AUTHOR(S): Adams, Julian; Palombella, Vito J.; Sausville, Edward A.; Johnson, Jill; Destree, Antonia; Lazarus, Douglas D.; Maas, Jochen; Pien, Christine S.; Prakash, Samuel; Elliott, Peter J.
CORPORATE SOURCE: ProScript, Inc., Cambridge, MA, 02139, USA
SOURCE: Cancer Research (**1999**), 59(11), 2615-2622
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ubiquitin-proteasome pathway plays a critical role in the **regulated** degradation of proteins involved in cell cycle control and tumor growth. Dysregulating the degradation of such proteins should have profound effects on tumor growth and cause cells to undergo apoptosis. To test this hypothesis, we developed a novel series of proteasome inhibitors, exemplified by PS-341, which we describe here. As determined by the National Cancer Institute in vitro screen, PS-341 has substantial cytotoxicity against a broad range of human tumor cells, including prostate cancer cell lines. The PC-3 prostate cell line was, therefore, chosen to further examine the antitumor activity of PS-341. In vitro, PS-341 elicits proteasome inhibition, leading to an increase in the intracellular levels of specific proteins, including the cyclin-dependent **kinase** inhibitor, p21. Moreover, exposure of such cells to PS-341 caused them to accumulate in the G2-M phase of the cell cycle and subsequently undergo apoptosis, as indicated by nuclear condensation and poly(ADP-ribose) polymerase cleavage. Following weekly i.v. treatment of PS-341 to mice bearing the PC-3 tumor, a significant decrease (60%) in tumor burden was observed in vivo. Direct injection of PS-341 into the tumor also caused a substantial (70%) decrease in tumor volume with 40% of the drug-treated mice having no detectable tumors at the end of the study. Studies also revealed that i.v. administration of PS-341 resulted in a rapid and widespread distribution of PS-341, with highest levels identified in the liver and gastrointestinal tract and lowest levels in the skin and muscle. Modest levels were found in the prostate, whereas there was no apparent penetration of the central nervous system. An assay to follow the biol. activity of the PS-341 was established and used to determine temporal drug activity as well as its ability to penetrate tissues. As such, PS-341 was shown to penetrate PC-3 tumors and inhibit intracellular proteasome activity 1.0 h after i.v. dosing. These data illustrate that PS-341 not only reaches its biol. target but has a direct effect on its biochem. target, the proteasome. Importantly, the data show that inhibition of this target site by PS-341 results in reduced tumor growth in murine tumor models. Together, the results highlight that the proteasome is a novel biochem. target and that inhibitors such as PS-341 represent a unique class of antitumor agents. PS-341 is currently under clin. evaluation for advanced cancers.

IT **179324-69-7**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of potent, selective and reversible dipeptide boronic acid proteasome inhibitors as antitumor agents)

RN 179324-69-7 HCAPLUS
CN Boronic acid, [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 27 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:293146 HCAPLUS
DOCUMENT NUMBER: 131:141356
TITLE: Enzyme kinetic characterization of the smooth muscle myosin phosphorylating system: activation by calcium and calmodulin and possible inhibitory mechanisms of antagonists
AUTHOR(S): Sobieszek, Apolinary
CORPORATE SOURCE: Institute of Molecular Biology, Austrian Academy of Sciences, Salzburg, A-5020, Austria
SOURCE: Biochimica et Biophysica Acta (**1999**), 1450(1), 77-91
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

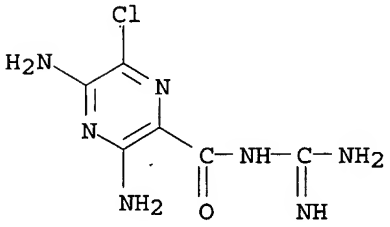
AB A native-like smooth muscle filamentous myosin system was characterized from an enzyme kinetic point of view. The system contains endogenous myosin light chain **kinase** (MLCKase) and calmodulin (CM) and is, therefore, well suited for testing the action of CM-antagonists or other inhibitory compds. However, this has not been done due to its complexity. The characterization of the system includes: (1) derivation of a relationship for rate of myosin phosphorylation in terms of total CM, free Ca2+ and total MLCKase concns., which includes only three binding consts.; and (2) derivation of relationships between fractional inhibition rate (vi/vo) and total inhibitor concentration (It) which cover most of the inhibitory mechanisms applicable to the myosin system or to other CM-dependent enzymes. The three binding consts. were subsequently evaluated from exptl. data for filamentous myosin and for its isolated **regulatory** light chain (ReLC) using a non-linear regression software. They indicated differences in the interaction of myosin filament with the active CM-MLCKase complex in comparison to that of the isolated ReLC. The derived vi/vo vs. It relationships, together with the software, make it possible to evaluate the inhibition consts. and binding stoichiometries of CM-antagonists and other compds. inhibiting myosin phosphorylation. This approach was successfully applied to exptl. data on inhibition of MLCKase by amiloride, cadmium, or CM-binding peptide (M-12) for simple mechanisms. For more complex mechanisms, inhibition by calmidazolium, trifluoperazine or melittin, the anal. showed that only calmidazolium acted specifically at the CM level in a multiple-site activator-depletion mechanism. Melittin and trifluoperazine inhibited the phosphorylation rate by a novel substrate-and-activator depletion mechanism, in which addnl. inhibition of the substrate resulted in the removal of the inhibition at the lower range of the antagonists' concentration

IT **2609-46-3**, Amiloride

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kinetic characterization of the smooth muscle myosin phosphorylating system in relation to activation by calcium and calmodulin and possible inhibitory mechanisms of antagonists)

RN 2609-46-3 HCAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 28 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:294251 HCAPLUS

DOCUMENT NUMBER: 129:26310

TITLE: Calcium-sensitive particulate guanylyl cyclase as a modulator of cAMP in olfactory receptor neurons

AUTHOR(S): Moon, Cheil; Jaberi, Parham; Otto-Bruc, Annie; Baehr, Wolfgang; Palczewski, Krzysztof; Ronnett, Gabriele V.

CORPORATE SOURCE: Dep. Neurosci., Johns Hopkins Univ. Sch. Med., Baltimore, MD, 21205, USA

SOURCE: Journal of Neuroscience (**1998**), 18(9), 3195-3205
CODEN: JNRSDS; ISSN: 0270-6474

PUBLISHER: Society for Neuroscience

DOCUMENT TYPE: Journal

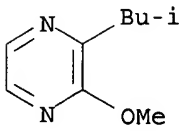
LANGUAGE: English

AB The second messengers cAMP and inositol 1,4,5-triphosphate have been implicated in olfaction in various species. The odorant-induced cGMP response was investigated using cilia prepns. and olfactory primary cultures. Odorants cause a delayed and sustained elevation of cGMP. A component of this cGMP response is attributable to the activation of one of two kinetically distinct cilial receptor guanylyl cyclases by calcium and a guanylyl cyclase-activating protein (GCAP), cGMP thus formed serves to augment the cAMP signal in a cGMP-dependent protein **kinase** (PKG) manner by direct activation of adenylate cyclase. CAMP, in turn, activates cAMP-dependent protein **kinase** (PKA) to neg. **regulate** guanylyl cyclase, limiting the cGMP signal. These data demonstrate the existence of a **regulatory** loop in which cGMP can augment a cAMP signal, an in turn cAMP neg. **regulates** cGMP production via PKA. Thus, a small, localized, odorant-induced cAMP response may be amplified to **modulate** downstream transduction enzymes or transcriptional events.

IT **142008-29-5**, Protein **kinase** A
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(calcium-sensitive particulate guanylyl cyclase as **modulator** of cAMP in olfactory receptor neurons)

RN 142008-29-5 HCAPLUS
CN Kinase (phosphorylating), protein, A (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **24683-00-9 141588-27-4**, Protein **kinase** G
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(calcium-sensitive particulate guanylyl cyclase as **modulator** of cAMP in olfactory receptor neurons)
RN 24683-00-9 HCAPLUS
CN Pyrazine, 2-methoxy-3-(2-methylpropyl)- (9CI) (CA INDEX NAME)



RN 141588-27-4 HCAPLUS
CN Kinase (phosphorylating), protein, G (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

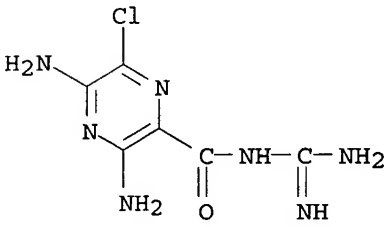
L23 ANSWER 29 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:613118 HCAPLUS
DOCUMENT NUMBER: 127:257356
TITLE: Modulation of cytokine production and protection against lethal endotoxemia by the cardiac glycoside ouabain
AUTHOR(S): Matsumori, Akira; Ono, Koh; Nishio, Ryosuke; Igata, Hideki; Shioi, Tetsuo; Matsui, Shigeo; Furukawa, Yutaka; Iwasaki, Atsushi; Nose, Yoshisuke; Sasayama, Shigetake
CORPORATE SOURCE: Department of Cardiovascular Medicine, Kyoto University, Kyoto, 606, Japan
SOURCE: Circulation (**1997**), 96(5), 1501-1506
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies have shown that cytokines are capable of **modulating** cardiovascular function and that some drugs used in the treatment of heart failure variably **modulate** the production of cytokines. To examine whether cardiac glycosides also **modulate** cytokine production, we evaluated the effects of ouabain on the production of cytokines in vitro and in vivo. Human peripheral blood mononuclear cells (PBMC) were obtained from healthy volunteers. PBMC were cultured with or without ouabain in the presence or absence of lipopolysaccharide (LPS). Ouabain induced the production of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α in PBMC and induced mRNA of these cytokines, an induction apparently at the transcriptional level. Amiloride, staurosporin, and genistein inhibited cytokine production, and protein **kinase** C and tyrosine **kinase** appeared to be involved in the **modulation** of cytokine production induced by ouabain. However, when PBMC were stimulated with LPS, ouabain suppressed the production of IL-6 and TNF-α. To investigate whether ouabain **modulates** cytokine

production in vivo, we evaluated the effects of ouabain in LPS-treated mice. Ouabain was found to protect against LPS-induced lethal toxicity in mice and decreased circulating IL-6 and TNF-α levels in vivo. These previously unrecognized immunomodulating effects of a cardiac glycoside may explain either the beneficial or the detrimental effects of these drugs in heart failure patients.

IT **2609-46-3**, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(modulation of cytokine production and protection against lethal endotoxemia by cardiac glycoside ouabain)

RN 2609-46-3 HCAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



IT **80449-02-1**, Tyrosine **kinase** 141436-78-4, Protein **kinase** C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**modulation** of cytokine production and protection against lethal endotoxemia by cardiac glycoside ouabain)

RN 80449-02-1 HCAPLUS

CN Kinase (phosphorylating), protein (tyrosine) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 141436-78-4 HCAPLUS

CN Kinase (phosphorylating), protein, cPKC (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 30 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:581506 HCAPLUS

DOCUMENT NUMBER: 127:260830

TITLE: Loss of protein kinase C inhibition in the β-T594M variant of the amiloride-sensitive Na+ channel

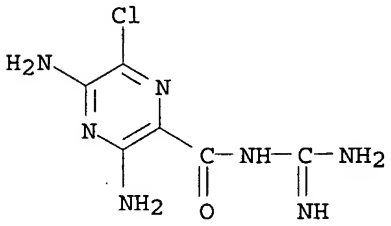
AUTHOR(S): Cui, Yong; Su, Yan Ru; Rutkowski, Mark; Reif, Max; Menon, Anil G.; Pun, R. Y. K.

CORPORATE SOURCE: Departments Molecular Genetics, Biochemistry, and Microbiology, Internal Medicine, Division Nephrology and Hypertension, Molecular and Cellular Physiology, College Medicine, Univ. Cincinnati, Cincinnati, OH, 45267-0576, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1997**), 94(18), 9962-9966
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal
LANGUAGE: English
AB We previously reported the presence of a novel variant (β-T594M) of the amiloride-sensitive Na+ channel (ASSC) in which the threonine residue at position 594 in the β-subunit has been replaced by a methionine residue. Electrophysiol. studies of the ASSC on Epstein-Barr virus (EBV)-transformed lymphocytes carrying this variant showed that the 8-(4-chlorophenylthio) adenosine 3':5'-cyclic monophosphate (8cpt-cAMP)-induced responses were enhanced when compared to wild-type EBV-transformed lymphocytes. Furthermore, in wild-type EBV-transformed cells, the 8cpt-cAMP-induced response was totally blocked by the phorbol ester, phorbol 12-myristate 13-acetate (PMA). This inhibitory effect of PMA was blocked by a protein **kinase** C inhibitor, chelerythrine. We now have identified individuals who are homozygous for this variant, and showed that PMA had no effect on the 8cpt-cAMP-induced responses in the EBV-transformed lymphocytes from such individuals. Cells heterozygous for this variant showed mixed responses to PMA, with the majority of cells partially inhibited by PMA. Our results demonstrate than an alteration in a single amino acid residue in the β-subunit of the ASSC can lead to a total loss of inhibition to PMA, and establish the β-subunit as having an important role in conferring a **regulatory** effect on the ASSC of lymphocytes.
IT **2609-46-3**, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(loss of protein kinase C inhibition in β-T594M variant of amiloride-sensitive Na+ channel)
RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

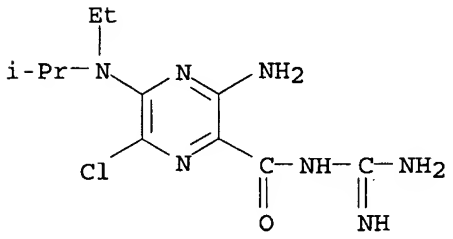
L23 ANSWER 31 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:438172 HCAPLUS
DOCUMENT NUMBER: 127:130667
TITLE: Short-term inhibition of the Na-H exchanger limits acidosis and reduces ischemic injury in the rat heart
AUTHOR(S): Schaefer, Saul; Ramasamy, Ravichandran
CORPORATE SOURCE: Division of Cardiovascular Medicine, University of California Davis, TB 172, Davis, CA, 95616, USA
SOURCE: Cardiovascular Research (**1997**), 34(2), 329-336
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pharmacol. inhibition of the Na-H exchanger prior to and during ischemia

has been shown to protect the ischemic heart by reducing Na-H exchange. However, pH **regulation** in the ischemic heart is primarily mediated by other pH **regulatory** mechanisms, such as metabolite efflux and sodium-coupled HCO3- influx, which may compensate for a reduction in Na-H exchange by increasing proton efflux. We hypothesized that short-term pharmacol. inhibition of the Na-H exchanger would result in increases in other compensatory pH **regulatory** mechanisms and thereby limit acidosis during ischemia and reduce ischemic injury. In order to test this hypothesis, we exposed isolated perfused rat hearts to ethylisopropylamiloride (EIPA, 3 μM) for 40 min, followed by 10 min of EIPA-free perfusate and 30 min of global ischemia (termed CTL/EIPA hearts). The effects of this intervention were compared to hearts perfused with either glucose alone (CTL) or EIPA 3 μM for 10 min before ischemia (EIPA). Ischemic injury was measured using creatine **kinase** (CK) release on reperfusion, while pH and metabolic effects were measured using 31P NMR spectroscopy. The effect of this intervention on recovery from an acid load was assessed using an NH4Cl pre-pulse in bicarbonate-containing Krebs-Henseleit as well as HEPES buffer. Both CTL/EIPA and EIPA hearts had marked reduction in ischemic injury (CK control 1191 ± 116 IU/g dry weight; CTL/EIPA 406 ± 42 IU/gdw; EIPA 333 ± 78 IU/gdw), as well as significantly reduced end-diastolic pressure on reperfusion. Intracellular pH was higher in the CTL/EIPA hearts (end-ischemic pH = 6.34 ± 0.05) compared to either control (5.86 ± 0.02) or EIPA hearts (6.01 ± 0.02), while pH recovery on reperfusion was markedly slowed in the CTL/EIPA hearts. CTL/EIPA hearts had rapid ATP depletion during ischemia, but PCr recovery comparable to EIPA hearts. Acidification on exposure to NH4Cl was increased in the presence of HEPES, but pH recovery was not altered by short-term exposure to EIPA. These data show that short-term inhibition of the Na-H exchanger altered pH **regulation** in the ischemic heart, resulting in reduced acidosis and slow pH recovery on reperfusion, coupled with reduction in ischemic injury and end-diastolic pressure on reperfusion. These findings are consistent with short-term exposure to EIPA accelerating ATP depletion during ischemia, as well as limiting proton efflux during reperfusion.

IT **1154-25-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Na-H exchanger inhibition by ethylisopropylamiloride limits acidosis and ischemic damage)

RN 1154-25-2 HCAPLUS

CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-[ethyl(1-methylethyl)amino]- (9CI) (CA INDEX NAME)



L23 ANSWER 32 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:526284 HCAPLUS
DOCUMENT NUMBER: 125:193392
TITLE: Differential regulation of cell cycle machinery by

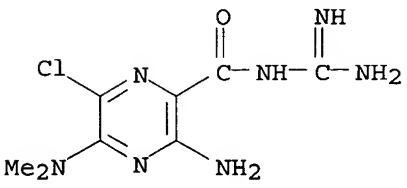
	various antiproliferative agents is linked to macrophage arrest at distinct G1 checkpoints
AUTHOR(S):	Vadiveloo, Peter K.; Vairo, Gino; Novak, Ulrike; Royston, A. Keith; Whitty, Genevieve; Filonzi, Enrico L.; Cragoe, Edward J., Jr.; Hamilton, John A.
CORPORATE SOURCE:	Royal Melbourne Hospital, University of Melbourne, Parkville, 3050, Australia
SOURCE:	Oncogene (**1996**), 13(3), 599-608 CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER:	Stockton
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB There is currently much interest in the mechanisms of action of antiproliferative agents and their effects on cell cycle machinery. In the present study we examined the mechanisms of action of four unrelated agents known to inhibit proliferation of CSF-1-stimulated bone marrow-derived macrophages (BMM). We report that 8-bromo-cAMP (8Br-cAMP) and lipopolysaccharide (LPS) potently reduced CSF-1-stimulated cyclin D1 protein, and cyclin-dependent kinase (cdk) 4 mRNA and protein levels, while the inhibitory effects of the Na+/H+ antiport inhibitor 5-(N',N'-dimethyl) amiloride (DMA) and interferon gamma (IFNγ) were only weak. All agents repressed CSF-1-simulated retinoblastoma protein phosphorylation. Furthermore, 8Br-cAMP and to a lesser extent IFNγ, also reduced CSF-1-stimulated levels of E2F DNA binding activity in a macrophage cell line, BAC1.2F5. An explanation for the different effects of the agents is that 8Br-cAMP and LPS were found to arrest BMM in late G1 or early S phase. These data indicate that (1) different antiproliferative agents can arrest the same cell type at distinct checkpoints in G1 and (2) effects of antiproliferative agents on cell cycle machinery is linked to the position at which they arrest cells in G1.

IT **1214-79-5**, 5-Dimethylamiloride
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(differential regulation of cell cycle machinery by various antiproliferative agents is linked to macrophage arrest at G1 checkpoints)

RN 1214-79-5 HCAPLUS

CN Pyrazinecarboxamide, 3-amino-N-(aminoiminomethyl)-6-chloro-5-(dimethylamino)- (9CI) (CA INDEX NAME)



IT **147014-97-9**, Cyclin-dependent **kinase** 4
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(differential **regulation** of cell cycle machinery by various antiproliferative agents is linked to macrophage arrest at G1 checkpoints)

RN 147014-97-9 HCAPLUS

CN Kinase (phosphorylating), protein p33CDK4 (9CI) (CA INDEX NAME)

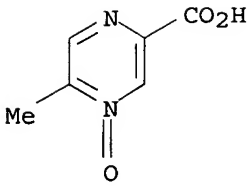
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L23 ANSWER 33 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:138502 HCAPLUS
DOCUMENT NUMBER: 124:220159
TITLE: Mechanism of anti-lipolytic action of acipimox in isolated rat adipocytes
AUTHOR(S): Christie, A. W.; McCormick, D. K. T.; Emmison, N.; Kraemer, F. B.; Alberti, K. G. M. M.; Yeaman, S. J.
CORPORATE SOURCE: Department Biochemistry and Genetics, University Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, UK
SOURCE: Diabetologia (**1996**), 39(1), 45-53
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acipimox is commonly used to treat hypertriglyceridemia in non-insulin-dependent diabetic patients, but its precise mechanism of action has yet to be elucidated. The authors examined the in vitro effects of acipimox on the lipolytic **regulatory** cascade in epididymal adipocytes isolated from Wistar rats. Acipimox inhibited the lipolytic rate stimulated by adenosine deaminase (1 U/mL) in a concentration-dependent manner, reaching a near-basal value at 10 μmol/l acipimox. Lipolysis activated by sub-maximal levels of isoproterenol in combination with adenosine deaminase (20 mU/mL) was significantly decreased by 100 μmol/l acipimox, whereas, in the absence of adenosine deaminase, 100 μmol/l acipimox showed no significant inhibition. These findings suggested that the anti-lipolytic mechanism **regulated** by adenosine may also be **regulated** by acipimox. Acipimox diminished the intracellular cAMP level produced by 25 nmol/l isoproterenol in the presence of adenosine deaminase (20 mU/mL) in a concentration-dependent manner. At the same level of stimulation, acipimox inhibited the cAMP-dependent protein **kinase** activity ratio and lipolytic rate over the same concentration range, with significant redns. occurring at and above, 0.5 μmol/l and 10 μmol/l acipimox, resp. Western blotting showed that upon lipolytic stimulation (1 U/mL adenosine deaminase; 100 nmol/l isoproterenol) a threefold increase in the lipolytic rate was accompanied by a significant rise in hormone-sensitive lipase associated with the lipid fraction. Acipimox (1 mmol/l) and insulin (1 nmol/l) re-distributed hormone-sensitive lipase back to the cytosol, with a corresponding significant loss from the fat cake fraction of adipocyte homogenates. In conclusion, the anti-lipolytic action of acipimox is mediated through suppression of intracellular cAMP levels, with the subsequent decrease in cAMP-dependent protein **kinase** activity, leading to the reduced association of hormone-sensitive lipase with triacylglycerol substrate in the lipid droplet of adipocytes.

IT **51037-30-0**, Acipimox
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of anti-lipolytic action of acipimox in isolated rat adipocytes)

RN 51037-30-0 HCAPLUS
CN Pyrazinecarboxylic acid, 5-methyl-, 4-oxide (9CI) (CA INDEX NAME)

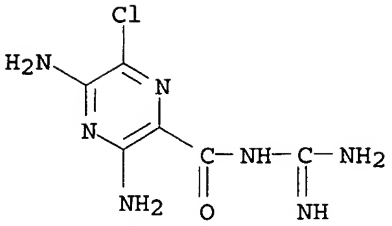


L23 ANSWER 34 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:670270 HCAPLUS
DOCUMENT NUMBER: 123:102196
TITLE: Amiloride modulates urokinase gene expression at both transcription and post-transcription levels in human colon cancer cells
AUTHOR(S): Wang, Yao; Dang, Jinjun; Liang, Xiaoming; Doe, William F.
CORPORATE SOURCE: John Curtin School Medical Research, Australian National University, Canberra, ACT 2601, Australia
SOURCE: Clinical & Experimental Metastasis (**1995**), 13(3), 196-202
CODEN: CEXMD2; ISSN: 0262-0898
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activity of receptor-bound urokinase plasminogen activator (uPA) on the surface of colon cancer cells appears to be a function of the number of uPA receptors. The regulation of uPA therefore may determine the invasive phenotype. The effects of amiloride on the modulation of uPA mRNA and protein induced by phorbol ester (PMA) and cycloheximide (CHX) were studied in four colon cancer cell lines, HCT116, KM12SM, LIM1215 and LS123. Northern blot analyses showed that PMA induced uPA mRNA that peaked at 2-48 h in HCT116 cells. In all colon cancer cell lines tested, the expression of uPA mRNA by PMA was super-induced after the addition of the protein synthesis inhibitor CHX, suggesting that stimulation of uPA gene expression does not require de novo protein synthesis. UPA mRNA was also induced by CHX alone, indicating that there may be a labile protein which inhibits uPA mRNA processing. Amiloride profoundly inhibited uPA mRNA production at concns. between 0.1-1 mM in the presence or absence of PMA or CHX. UPA protein levels on the colon cancer cell surface reflected PMA induction and amiloride inhibition of uPA mRNA levels. Transcriptional elongation expts. using isolated nuclei indicated that while the induction effects of PMA or CHX on uPA gene expression were mediated at the post-transcriptional level, amiloride acted at both transcription and post-transcription levels. The inhibitory effects of amiloride on uPA gene expression reported in this paper may offer the prospect of developing new therapeutic approaches to the prevention of invasion and metastasis by adenocarcinomas.

IT **2609-46-3**, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amiloride modulates urokinase gene expression at both transcription and post-transcription levels in human colon cancer cells)

RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



IT **9039-53-6**, Urokinase plasminogen activator
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(amiloride **modulates** urokinase gene expression at both transcription and post-transcription levels in human colon cancer cells)
RN 9039-53-6 HCAPLUS
CN Kinase (enzyme-activating), uro- (9CI) (CA INDEX NAME)

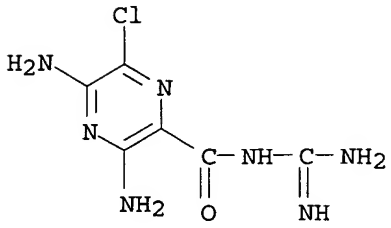
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L23 ANSWER 35 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:387162 HCAPLUS
DOCUMENT NUMBER: 122:178167
TITLE: Intrastriatal infusion of amiloride increases rotations in 6-OHDA lesioned rats and "down-regulates" D2 receptors in the striatum and 5-HT2A receptors in the cortex
AUTHOR(S): Jamrozik, Zygmunt; De Yebenes, Justo Garcia; Troung, Daniel D.; Cadet, Jean
CORPORATE SOURCE: Department of Neurology, Medical Academy, Warsaw, 02-097, Pol.
SOURCE: Polish Journal of Pharmacology (**1994**), 46(5), 417-22
CODEN: PJPAE3; ISSN: 1230-6002
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intrastriatal infusion of amiloride and 12-0-tetradecanoyl phorbol-13-acetate (TPA) in 6-OHDA lesioned rats increased the apomorphine (APO)-induced rotation. This behavioral effect occurred in the presence of a decrease in the d. and an increase in the affinity of D2 dopamine receptors in the striatum. There was an associated decrease in the number of 5-HT2A receptors labeled with ketanserin in the cortex on the side of infusion. These results suggest that the inositol second-messenger system may be involved in the regulation of D2-dopamine receptors in the striatum and dopamine mediated behavior in the 6-OHDA lesioned rats. They also indicate a possible role for the inositol second messenger system in the regulation of 5-HT2A receptors.
IT **141436-78-4**, Protein **kinase** C
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; intrastriatal amiloride increases rotations in 6-OHDA lesioned rats and down-**regulates** D2 receptors in striatum and 5-HT2A receptors in cortex)
RN 141436-78-4 HCAPLUS
CN Kinase (phosphorylating), protein, cPKC (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **2609-46-3**, Amiloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(intrastriatal amiloride increases rotations in 6-OHDA lesioned rats and down-regulates D2 receptors in striatum and 5-HT2A receptors in cortex)

RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)

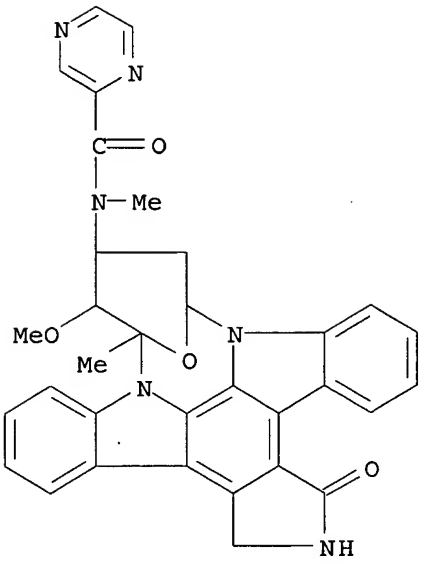


L23 ANSWER 36 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:548324 HCAPLUS
DOCUMENT NUMBER: 121:148324
TITLE: Inhibitory activity and selectivity of staurosporine derivatives towards protein kinase C
AUTHOR(S): Caravatti, Giorgio; Meyer, Thomas; Fredenhagen, Andreas; Trinks, Uwe; Mett, Helmut; Fabbro, Doriano
CORPORATE SOURCE: Oncol. Virol. Dep., Ciba-Geigy Ltd., Basel, CH-4002, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1994**), 4(3), 399-404
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and in vitro protein kinase C (PKC) inhibition of a series of staurosporine derivs. is described. Essential for activity is a free NH of the lactam portion of the mol. A large variety of substituents is tolerated at the secondary amine, although in most cases these modifications lead to a decrease in activity. Acylation of the methylamino group leads generally to the most selective derivs. with respect to other serine/threonine and tyrosine kinases. Selective inhibitors of protein kinase C may.

IT **155848-17-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and protein kinase inhibition by, structure in relation to)

RN 155848-17-2 HCAPLUS
CN Pyrazinecarboxamide, N-[(9S,10R,11R,13R)-2,3,10,11,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-lm]pyrrolo[3,4-g][1,7]benzodiazonin-11-yl]-N-methyl- (9CI) (CA INDEX NAME)



L23 ANSWER 37 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:512565 HCAPLUS
DOCUMENT NUMBER: 115:112565
TITLE: Characterization of guinea pig eosinophil phosphodiesterase activity. Assessment of its involvement in regulating superoxide generation
AUTHOR(S): Souness, John E.; Carter, Caroline M.; Diocee, Baljeet K.; Hassall, Giles A.; Wood, Lorna J.; Turner, Nicholas C.
CORPORATE SOURCE: Dagenham Res. Cent., Rhone-Poulenc Rorer Inc., Dagenham/Essex, RM10 7XS, UK
SOURCE: Biochemical Pharmacology (**1991**), 42(4), 937-45
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

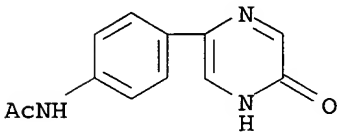
AB Expts. were performed to characterize guinea pig peritoneal eosinophil cyclic nucleotide phosphodiesterase (PDE) activity and establish whether it is involved in **regulating** superoxide (O2-) generation. Eosinophils were found to contain a predominantly membrane-bound cAMP PDE(s) (92.5% of total activity) which was resistant to solubilization with Triton X-100 (1%). This particulate PDE exhibited complex kinetics (Km = 1.3 and 31.4 μM) and was unaffected by cGMP (IC50>100 μM) or CaCl2 (2 mM) + calmodulin (10 units/mL). Little cGMP PDE activity as detected in either the soluble or particulate fractions. Inhibitors of the Ro-20-1724-inhibited (Type IV) cAMP PDE, namely Ro-20-1724 (IC50 = 0.92 μM), rolipram (IC50 = 0.20 μM) and denbufylline (IC50 = 0.20 μM), potently inhibited the particulate cAMP PDE, as did the non-selective inhibitors trequinsin (IC50 = 0.11 μM) and AH-21-132 (IC50 = 2.57 μM). Eosinophil cAMP PDE was resistant to SK&F 94120 (IC50>1000 μM), the cGMP-inhibited (Type III) cAMP PDE inhibitor, and the cGMP PDE (Type I) inhibitor, zaprinast, was only weakly active (IC50 = 35.33 μM). The O2- release from resting cells was potently inhibited by rolipram and denbufylline but surprisingly, in view of its potent cAMP PDE inhibitory activity, was only weakly decreased by trequinsin. AH-21-132, SK&F 94120, and zaprinast were without effect. Rolipram and denbufylline

alone exerted little effect on cAMP in intact cells but, in the presence of 10 μM isoprenaline, potently increased intracellular accumulation. Trequinsin and AH-21-132 only weakly enhanced isoprenaline-stimulated cAMP accumulation. Although it induced a marked rise in cAMP only in the presence of isoprenaline, rolipram alone could increase the activity ratio of cAMP-dependent protein **kinase** from 0.24 to 0.84. Thus, Ro-20-1724-inhibited cAMP PDE plays a role in **regulating** eosinophil O2- generation. The poor correlation between the PDE inhibitory actions of certain compds. and their effectiveness in elevating cAMP and inhibiting O2- suggests the existence of a barrier impeding access to the enzyme.

IT **89541-55-9**, SK&F 94120
RL: BIOL (Biological study)
(cAMP phosphodiesterase response to, of eosinophil, superoxide formation in relation to)

RN 89541-55-9 HCAPLUS

CN Acetamide, N-[4-(4,5-dihydro-5-oxopyrazinyl)phenyl]- (9CI) (CA INDEX NAME)

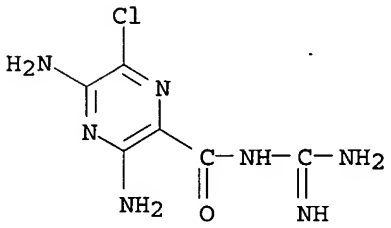


L23 ANSWER 38 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:154216 HCAPLUS
DOCUMENT NUMBER: 112:154216
TITLE: Calcium and calmodulin-sensitive inositol trisphosphate kinase from bovine parathyroid
AUTHOR(S): Conigrave, A. D.; Roufogalis, B. D.
CORPORATE SOURCE: Dep. Biochem., Univ. Sydney, Sydney, 2006, Australia
SOURCE: Cell Calcium (**1989**), 10(8), 543-50
CODEN: CECADV; ISSN: 0143-4160
DOCUMENT TYPE: Journal
LANGUAGE: English

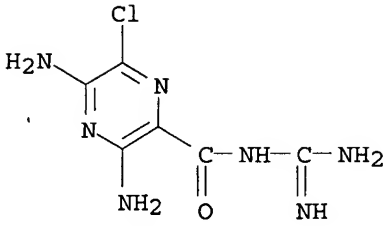
AB A Ca2+ and calmodulin-activated inositol 1,4,5-trisphosphate (IP3) **kinase** activity was detected in both soluble and membrane fractions from bovine parathyroid glands. Ca2+ activated the soluble enzyme in the concentration range 100 nM-1 μM, which corresponds to the Ca2+ concentration range observed in the intact cell following maximal variation in extracellular Ca2+, the principal **regulator** of parathyroid hormone release. The Ca2+ sensitivity of the enzyme was absolutely dependent upon calmodulin. A similar activity was detected in the membranes but could be progressively removed by repeated washing at low ionic strength. This, together with data demonstrating binding of the enzyme to the hydrophobic matrix, Ph-Sepharose, suggests that the association of the enzyme with the membrane is likely to involve a significant hydrophobic component. The organic base amiloride was identified as an inhibitor of the activity, the degree of inhibition being most marked in the presence of Ca2+ and calmodulin (K0.5 approx. 0.1 mM). The Ca2+ concentration dependence of the IP3 **kinase** suggests that inositol 1,3,4,5-tetrakisphosphate may be a messenger in the signal transduction pathway for the feedback inhibition of parathyroid hormone secretion by extracellular Ca2+.

IT **2609-46-3**, Amiloride
RL: BIOL (Biological study)

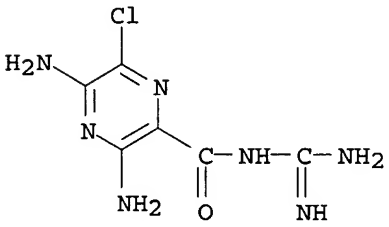
(inositol trisphosphate kinase of parathyroid gland inhibition by, kinetics of)
RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



L23 ANSWER 39 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:588274 HCAPLUS
DOCUMENT NUMBER: 111:188274
TITLE: Potentiation of the effects of atrial natriuretic factor on the cardiovascular system by amiloride
AUTHOR(S): Albus, U.; Linz, W.; Wiemer, G.; Knolle, J.; Breipohl, G.; Schoelkens, B. A.
CORPORATE SOURCE: Hoechst A.-G., Frankfurt/Main, D-6230/80, Fed. Rep. Ger.
SOURCE: Arzneimittel-Forschung (**1989**), 39(9), 1096-9
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amiloride has previously been shown to facilitate receptor binding of atrial natriuretic factor (ANF) to membranes of adrenal cortex and to enhance ANF-induced inhibition of steroid secretion in vitro. This interaction of amiloride and ANF also hold true for the cardiovascular system. In precontracted rabbit aortic strips, the relaxing effect induced by the combination of ANF (10-10 mol/L) and amiloride (10-5 mol/L) was more than additive. The production of cGMP, which parallels ANF induced relaxations of vascular strips, was not affected by amiloride alone up to 10-3 mol/L, but was concentration-dependently increased in the presence of ANF (10-8 mol/L). In spontaneously hypertensive rats, ANF-induced decreases in blood pressure were potentiated by amiloride. Post ischemia reperfusion arrhythmias in isolated rat hearts were reduced by ANF, and amiloride enhanced this effect. The binding expts. revealed an interaction of amiloride and ANF on the receptor level. Binding of labeled ANF to aortic tissue was concentration-dependently increased by amiloride. Addition of ATP had the opposite effect. Therefore, amiloride and ATP may interfere with a mechanism **regulating** the sensitivity of the vascular ANF-receptor for its ligand regarding binding and signal transforming, presumably by a **kinase**-mediated phosphorylation/dephosphorylation process.
IT **2609-46-3**, Amiloride
RL: BIOL (Biological study)
(cardiovascular system response to atriopeptin enhancement by)
RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



L23 ANSWER 40 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:529640 HCAPLUS
DOCUMENT NUMBER: 111:129640
TITLE: Inhibition of myosin light chain kinase by amiloride
AUTHOR(S): Higashihara, Masaaki
CORPORATE SOURCE: Fac. Med., Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Biochemical and Biophysical Research Communications (**1989**), 162(3), 1253-9
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphorylation of **regulatory** light chain (LC20) by myosin light-chain **kinase** (MLCK) has been thought to play an important role in both smooth muscle contraction and several functions of vertebrate nonmuscle cells. Amiloride, a frequently used Na+/H+ exchange inhibitor, potently inhibited phosphorylation of LC20 by MLCK. The inhibition was noncompetitive with respect to myosin but competitive with ATP (Ki = 0.95 μM), suggesting that amiloride may act as an ATP analog. Amiloride also inhibited the tension development of ether-treated gizzard fibers which were lacking in Na+/H+ antiport, even in the presence of an ATP regenerating system. Thus, it must be remembered that amiloride cannot be used as a specific inhibitor of Na+/H+ exchange, and that the inhibition of myosin phosphorylation by amiloride should be taken into consideration in studying the role of the Na+/H+ antiport in the cellular function.
IT **2609-46-3**, Amiloride
RL: BIOL (Biological study)
(myosin light chain kinase of smooth muscle inhibition by, kinetics of, proton-sodium exchange in relation to)
RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



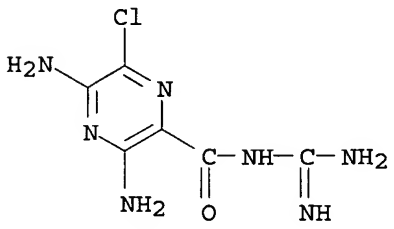
L23 ANSWER 41 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:563199 HCAPLUS
DOCUMENT NUMBER: 109:163199
TITLE: Amiloride enhances postischemic ventricular recovery:

possible role of sodium-proton exchange
AUTHOR(S): Karmazyn, Morris
CORPORATE SOURCE: Fac. Med., Dalhousie Univ., Halifax, NS, B3H 4H7, Can.
SOURCE: American Journal of Physiology (**1988**), 255(3, Pt. 2), H608-H615
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of amiloride (40 μg/mL) was studied in the isolated rat heart subjected to low-flow ischemia followed by reperfusion. Reperfusion after 30 min of ischemia produced recoveries of force, rate of force development (+dF/dt), and rate of relaxation (-dF/dt) of 42, 82, and 71%, resp., in control hearts. Amiloride did not enhance the maximum degree of recovery, although, when present during ischemia, it markedly shortened the time required for peak recovery. Reperfusion after 60 min of ischemia resulted in 18, 43, and 34% recovery of force, +dF/dt, and -dF/dt, resp. Amiloride enhanced recovery to a maximum of 39, 88, and 78% for force, +dF/dt, and -dF/dt, resp. The improved contractile recovery was accompanied by substantial redns. in the release of creatine **kinase** and 6-ketoprostaglandin F1α. Coronary perfusion pressure and resting tension were generally unaffected by amiloride, although there was a moderate tendency to attenuate these parameters after reperfusion. The salutary effects of amiloride were dependent on the drug's presence during ischemia, with maximum protection when it was administered during both ischemia and reperfusion and no benefit when added only at the time of reperfusion. Because of amiloride's well-documented property in inhibiting Na+-H+ exchange, it is possible that this process plays an important role in **modulating** the cardiac response to reperfusion.

IT **2609-46-3**, Amiloride
RL: BIOL (Biological study)
(heart ischemia response to, hydrogen ion-sodium exchange inhibition in)

RN 2609-46-3 HCAPLUS
CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



L23 ANSWER 42 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:161224 HCAPLUS
DOCUMENT NUMBER: 108:161224
TITLE: Effect of amiloride on regulatory mechanisms of vascular smooth muscle contraction
AUTHOR(S): Chatterjee, Meeta; Chiu, Peter J. S.; Doll, Ronald J.; Sybertz, Edmund J.
CORPORATE SOURCE: Pharm. Res. Div., Schering-Plough Corp., Bloomfield, NJ, 07003, USA
SOURCE: Biochemical Pharmacology (**1988**), 37(5), 813-18

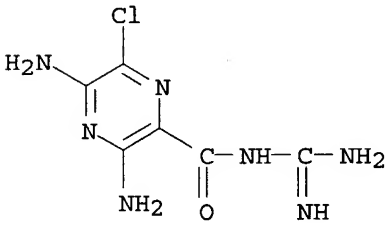
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expts. were conducted to characterize the effects of amiloride on the **regulatory** mechanisms of vascular smooth muscle contraction. Intact, saponin-skinned and A23187-treated strips of rabbit aorta were used for these studies. Amiloride reduced the norepinephrine bitartrate (NE)-stimulated increase in intracellular Ca2+ in intact arteries. In saponin-skinned arteries, amiloride depressed both stress and concomitant levels of myosin light-chain phosphorylation. This inhibition of stress appeared to be competitive with Mg-ATP. In A23187-treated prepns., where the effects of amiloride were studied at physiol. [Mg-ATP] in the absence of functional membrane Ca2+-channels, amiloride caused a reduction in both stress and myosin light-chain phosphorylation. In other expts. on intact arteries, the contractile response to phorbol 12,13-dibutyrate, an activator of protein **kinase** C, was reduced by amiloride. Apparently, the vasorelaxant effects of amiloride are mediated via inhibition of myosin light-chain **kinase** and protein **kinase** C, in addition to the inhibition of Ca2+ influx.

IT **2609-46-3**, Amiloride
RL: BIOL (Biological study)
(vasodilation from, myosin light-chain kinase and protein kinase C inhibition and calcium influx in)

RN 2609-46-3 HCAPLUS

CN Pyrazinecarboxamide, 3,5-diamino-N-(aminoiminomethyl)-6-chloro- (9CI) (CA INDEX NAME)



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